



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 320

[Docket No. FDA-2011-N-0830]

RIN 0910-AF97

Abbreviated New Drug Applications and 505(b)(2) Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is issuing a final rule to implement Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), which amended provisions of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) that govern the approval of 505(b)(2) applications and abbreviated new drug applications (ANDAs). This final rule implements portions of Title XI of the MMA that pertain to provision of notice to each patent owner and the new drug application (NDA) holder of certain patent certifications made by applicants submitting 505(b)(2) applications or ANDAs; the availability of 30-month stays of approval on 505(b)(2) applications and ANDAs that are otherwise ready to be approved; submission of amendments and supplements to 505(b)(2) applications and ANDAs; and the types of bioavailability and bioequivalence data that can be used to support these applications. This final rule also amends certain regulations regarding 505(b)(2) applications and ANDAs to facilitate compliance with and efficient enforcement of the FD&C Act.

DATES: This rule is effective [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket number found in brackets in the heading of this final rule into the “Search” box and follow the prompts, and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

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## I. Executive Summary

### I.A. Purpose of the Final Rule

This rule implements portions of Title XI of the MMA and revises and clarifies FDA regulations relating to 505(b)(2) applications and ANDAs in a manner intended to reduce unnecessary litigation, reduce delays in the approval of 505(b)(2) applications and ANDAs that are otherwise ready to be approved, and provide business certainty to both brand name and generic drug manufacturers.

Title XI of the MMA addressed two key concerns identified in a Federal Trade Commission (FTC) report on anticompetitive strategies that may delay access to generic drugs by: (1) Limiting the availability of 30-month stays of approval on 505(b)(2) applications and ANDAs that are otherwise ready to be approved and (2) establishing conditions under which a first applicant would forfeit the 180-day exclusivity period such that approval of subsequent ANDAs would no longer be blocked. FDA has been implementing the MMA directly from the statute since its enactment. Based on this experience, FDA is amending its regulations to

implement portions of the MMA that pertain to 30-month stays and other matters not related to forfeiture of 180-day exclusivity.

FDA is amending its regulations regarding 505(b)(2) applications and ANDAs to facilitate compliance with and efficient enforcement of the FD&C Act, and to clarify and update these regulations based on recent court decisions and our practical experience implementing provisions related to the approval of 505(b)(2) applications and ANDAs. For example, we are clarifying requirements for the NDA holder's description of the specific approved method of use claimed by the patent (the "use code") required for publication in FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (commonly known as the Orange Book) to address overbroad or ambiguous use codes that may delay approval of generic drugs. This clarification is intended to facilitate FDA's implementation of the statutory provisions that permit 505(b)(2) and ANDA applicants to omit ("carve out") protected conditions of use from labeling and obtain approval for conditions of use that are not covered by unexpired patents or exclusivity. We also are revising the regulations to codify the types of court decisions and other actions that will terminate a 30-month stay of approval on a 505(b)(2) application or ANDA. Finally, we are updating the regulations to codify FDA's current practice and policy and thereby promote transparency.

#### I.B. Summary of the Major Provisions of the Final Rule

##### I.B.1. Submission of Patent Information

The rule revises and streamlines requirements related to submission of patent information on: (1) Patents that claim the drug substance and/or drug product and meet the requirements for patent listing on that basis; (2) drug substance patents that claim only a polymorph of the active ingredient; and (3) certain NDA supplements.

We are codifying our longstanding requirement that the NDA holder's description of the patented method of use required for publication in the Orange Book must contain adequate information to assist FDA and 505(b)(2) and ANDA applicants in determining whether a listed method-of-use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval. To address overbroad or ambiguous use codes, we are expressly requiring that if the method(s) of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, the NDA holder's use code must describe only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the patent owner engaged in the manufacture, use, or sale of the drug product.

#### I.B.2. Timing of Submission of Patent Information

We are expressly describing our current practice with respect to listing patent information that has not been submitted to FDA within 30 days after patent issuance. Although we list untimely filed patents pursuant to section 505(c)(2) of the FD&C Act (21 U.S.C. 355(c)(2)), we generally do not require an applicant with a pending 505(b)(2) application or ANDA to provide a patent certification to the untimely filed patent. Thus, the untimely filed patent will neither delay approval of a pending 505(b)(2) application or ANDA until patent expiration nor necessitate a carve-out of information related to a patented method of use.

We are expanding the category of untimely filed patent information to include certain amendments to the NDA holder's description of the approved method(s) of use claimed by the patent, if such changes are not submitted: (1) Within 30 days of patent issuance; (2) within 30 days of approval of a corresponding change to product labeling; or (3) within 30 days of a decision by the U.S. Patent and Trademark Office (USPTO) or a Federal court that is specific to

the patent and alters the construction of a method-of-use claim(s) of the patent. This revision to our regulations is intended to reduce delays in approval related to overbroad or ambiguous patent use codes.

In addition, we are establishing that the submission date of patent information provided by an NDA holder after approval will be the earlier of the date on which Form FDA 3542 is date-stamped by the Central Document Room or officially received by FDA in an electronic format. These revisions are intended to facilitate prompt listing in the Orange Book and to remove any ambiguity about the date of submission in light of the implications of untimely filed patent information for the patent certification obligations of 505(b)(2) and ANDA applicants that rely upon the listed drug.

#### I.B.3. Correction or Change of Patent Information

We are clarifying and improving the procedures that govern challenges to the accuracy or relevance of the NDA holder's submission of patent information to the Agency. These procedures allow a person (including a 505(b)(2) or ANDA applicant) to request, for example, that an NDA holder confirm that a previously submitted use code complies with current requirements. We are establishing a 30-day timeframe in which the NDA holder will be required to substantively respond to the patent listing dispute and verify the accuracy and completeness of the response. We intend to take an incremental approach and evaluate whether FDA's revisions to the regulations on submission of method-of-use patent information and patent listing dispute procedures adequately address the problem of overbroad and ambiguous use codes before we determine whether a process to review a proposed labeling carve-out with deference to the 505(b)(2) and/or ANDA applicant(s)' interpretation of the scope of the patent is also needed.

In addition, we are expressly requiring the correction or change of patent information by the NDA holder if: (1) The patent or patent claim no longer meets the statutory requirements for listing; (2) the NDA holder is required by court order to amend patent information or withdraw a patent from the list; or (3) the term of a listed patent is extended under patent term restoration provisions. These revisions facilitate implementation of the MMA provision related to patent withdrawal and efficient enforcement of the FD&C Act.

#### I.B.4. Notice of Paragraph IV Certification--Timing

We are revising our regulations to clearly delineate the two limitations on the timeframe within which notice of a paragraph IV certification can be provided to the NDA holder and each patent owner: (1) The date before which notice may not be given (reflecting FDA's longstanding practice regarding premature notice) and (2) the date, established by MMA, by which notice must be given to be considered timely.

For an original application, a 505(b)(2) applicant must send notice of a paragraph IV certification on or after the date on which the 505(b)(2) application is filed and an ANDA applicant must send notice of a paragraph IV certification on or after the date on which it receives a "paragraph IV acknowledgment letter" from FDA stating that the application is sufficiently complete to permit a substantive review. Both 505(b)(2) and ANDA applicants must send notice of a paragraph IV certification not later than 20 days after the date of the "postmark" (as defined in this final rule) on the paragraph IV acknowledgment letter.

For an amendment or supplement, an applicant must send notice of a paragraph IV certification contained in an amendment to a 505(b)(2) application (that has been filed) or ANDA (that has been received for substantive review) or in a supplement to an approved application at the same time that the amendment or supplement is submitted to FDA.



We are establishing a date (the first working day after the day the patent is published in the Orange Book) before which an ANDA applicant cannot send valid notice of a paragraph IV certification to a newly listed patent. Notice of a paragraph IV certification that has been sent prematurely is invalid, and will not be considered to comply with the FD&C Act's notice requirement. This approach is intended to promote equity among ANDA applicants seeking eligibility for 180-day exclusivity and to reduce the burden on industry and FDA associated with serial submissions and multiple notices of paragraph IV certifications related to a newly issued patent.

#### I.B.5. Notice of Paragraph IV Certification--Content and Methods

We are revising the content of notice of a paragraph IV certification to incorporate requirements added by the MMA and to support the efficient enforcement of our regulations. We are also expanding the acceptable methods of sending notice of a paragraph IV certification beyond registered or certified mail to include "designated delivery services." This reduces the burden on 505(b)(2) and ANDA applicants who currently must submit requests to the Agency to send notice by common alternate delivery methods.

#### I.B.6. Amended Patent Certifications

We are clarifying the requirements for a 505(b)(2) or ANDA applicant to amend a paragraph IV certification after a judicial finding of patent infringement to reflect statutory changes made by the MMA. We are also clarifying the circumstances and timeframe in which a 505(b)(2) or ANDA applicant must submit an amended patent certification after an NDA holder has withdrawn a patent and requested removal of the patent from the Orange Book. The rule codifies our current practice of not removing a withdrawn patent from the list until FDA has determined that no first applicant is eligible for 180-day exclusivity or the 180-day exclusivity

period based on that patent has expired or has been extinguished, and exempting 505(b)(2) applicants from providing or maintaining a certification to withdrawn patents. In addition, the rule expressly codifies the current requirement for a 505(b)(2) or ANDA applicant to submit a patent certification to a timely filed, newly issued patent that claims the listed drug or an approved method of using such drug.

#### I.B.7. Patent Certification Requirements for Amendments

We are clarifying and augmenting the patent certification requirements for amendments to 505(b)(2) applications and ANDAs to ensure that certain types of changes to the drug product are accompanied by an appropriate patent certification (or recertification) or statement. An appropriate patent certification (or recertification) or statement is required to accompany an amendment to add a new indication or other condition of use, to add a new strength, to make other-than-minor changes in product formulation, or to change the physical form or crystalline structure of the active ingredient. The regulations continue to require that a patent certification be amended if, at any time before approval, the applicant learns that the previously submitted patent certification or statement is no longer accurate.

#### I.B.8. Limitation on Submission of Certain Amendments and Supplements to a 505(b)(2) Application or ANDA

We are codifying our current interpretation of the MMA's prohibition on submitting an amendment or a supplement to seek approval of: (1) "[A] drug that is a different drug" than the drug identified in the original 505(b)(2) application; or (2) "a drug referring to a different listed drug" than the drug cited as the basis for ANDA submission. We are implementing these parallel restrictions on submission of certain types of changes in an amendment or a supplement

to a 505(b)(2) application or ANDA in a manner that is consistent with the statutory text and preserves a meaningful opportunity for a single 30-month stay.

#### I.B.9. 505(b)(2) Applications

We are requiring a 505(b)(2) applicant to identify one pharmaceutically equivalent drug product approved in an NDA, if one or more is approved before the original 505(b)(2) application is submitted, as a listed drug relied upon, and comply with applicable regulatory requirements. This is intended to help ensure that the 505(b)(2) pathway is not used to circumvent the statutory patent certification obligations that would have applied if the proposed product could have been approved in an ANDA.

#### I.B.10. Date of Approval of a 505(b)(2) Application or ANDA

The rule describes, in a more comprehensive manner, the timing of approval of a 505(b)(2) application or ANDA based on the patent certification(s) or statement(s) submitted by the 505(b)(2) or ANDA applicant. We are revising the regulations to reflect the MMA's limitation on multiple 30-month stays of approval of a 505(b)(2) application or an ANDA containing a paragraph IV certification to certain patents.

We are clarifying that the statutory 30-month stay begins on the later of the date of receipt of notice of paragraph IV certification by any owner of the listed patent or by the NDA holder (or its representative(s)). This revision codifies our current practice and provides an efficient means of ensuring that each patent owner or NDA holder receives the full statutory 30-month stay.

We are codifying the MMA's amendments that clarify the type of Federal district and appellate court decisions in patent litigation that will terminate a 30-month stay and lead to approval of a 505(b)(2) application or ANDA that is otherwise eligible for approval. We are also

addressing other scenarios in which a 30-month stay may be terminated, including written consent to approval by the patent owner or exclusive patent licensee, a court order terminating the stay, or a court order of dismissal without a finding of infringement in each pending suit for patent infringement brought within 45 days of receipt of the notice of paragraph IV certification. These clarifications are intended to avoid unnecessary delays in approval of 505(b)(2) applications and ANDAs while upholding the statutory purpose of the stay (i.e., to allow time for patent infringement claims to be litigated prior to approval of the potentially infringing product).

#### I.B.11. Notification of Commercial Marketing

We are updating the regulations to reflect the MMA provisions that modify the types of events that can trigger the start of the 180-day exclusivity period. A first applicant is required to submit correspondence to its ANDA notifying FDA within 30 days of the date of first commercial marketing of the drug product. If a first applicant does not notify FDA within this timeframe, we are deeming the date of first commercial marketing to be the date of the drug product's approval. This may have the effect of shortening the 180-day exclusivity period in a similar manner to the current regulatory consequence for failure to provide "prompt" notice of first commercial marketing.

#### I.B.12. Notification of Court Actions or Written Consent to Approval

We are expanding the scope of documentation that an applicant must submit to FDA regarding patent-related court actions and written consent to approval to ensure that FDA is promptly advised of information that may affect the timing of approval of a 505(b)(2) application or ANDA.

### I.C. Legal Authority

Title XI of the MMA and sections 505, 505A, 505E, and 527 of the FD&C Act (21 U.S.C. 355, 355a, 355f, and 360cc), in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act (21 U.S.C. 371(a)), serve as our principal legal authority for this rule.

#### I.D. Costs and Benefits

Many provisions of this final rule codify current practice, but some elements will lead to changes that generate additional benefits and costs. The table summarizes the benefits and costs of this final rule. The estimated annualized monetized benefits of this final rule are \$215,247 at a 3 percent or 7 percent discount rate, while the estimated annualized monetized costs are \$266,947 at a 3 percent discount rate and \$275,925 at a 7 percent discount rate. We have also identified, but are unable to quantify, additional impacts from changes to submitted patent information.

Summary of Benefits and Costs

	Benefits	Costs
One-time (Year 1) Cost for Reading the Rule	Not Applicable	\$466,450
Annually Recurring Compliance Costs or Savings (Years 1-10)	\$215,247	\$213,858
Present Value at 3 Percent	\$1,836,098	\$2,277,116
Present Value at 7 Percent	\$1,511,803	\$1,937,983
Annualized Value at 3 Percent	\$215,247	\$266,947
Annualized Value at 7 Percent	\$215,247	\$275,925

## II. Table of Abbreviations and Acronyms Commonly Used in This Document

Abbreviation	What it Means
ANDA	Abbreviated New Drug Application
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CSA	Controlled Substances Act
ESG	Electronic Submissions Gateway
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	U.S. Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
FOIA	Freedom of Information Act
FR	Federal Register
FTC	U.S. Federal Trade Commission
GAIN	Generating Antibiotic Incentives Now
GDUFA	Generic Drug User Fee Amendments of 2012
IRTNMTA	Improving Regulatory Transparency for New Medical Therapies Act

Abbreviation	What it Means
MMA	Medicare Prescription Drug, Improvement, and Modernization Act of 2003
NDA	New Drug Application
OGD	Office of Generic Drugs (in FDA's Center for Drug Evaluation and Research)
OMB	U.S. Office of Management and Budget
OND	Office of New Drugs (in FDA's Center for Drug Evaluation and Research)
Orange Book	FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations"
OTC	Over-the-counter
RLD	Reference Listed Drug
U.S.	United States
U.S.C.	United States Code
USPS	United States Postal Service
USPTO	U.S. Patent and Trademark Office

### III. Background

The 505(b)(2) application and ANDA approval pathways were enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (Hatch-Waxman Amendments). The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962" with new incentives for drug development in the form of marketing exclusivity and patent term extensions (see H. Rept. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S. Code Congressional and Administrative News 2647 at 2647-2648).

A 505(b)(2) application is an NDA that contains full reports of investigations of safety and effectiveness, where at least some of the information relied upon by the applicant for approval of the NDA comes from investigations that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (e.g., published literature or the Agency's finding of safety and/or effectiveness for one or more listed drugs) (see section 505(b)(2) of the FD&C Act; compare section 505(b)(1) of the FD&C Act for "stand-alone" NDAs).

An ANDA contains information to show that the proposed product is the same as a previously approved drug (the reference listed drug or RLD) with respect to active ingredient, conditions of use, dosage form, route of administration, strength, and (with certain permissible differences) labeling, among other characteristics. An ANDA applicant also must demonstrate that its proposed drug product is bioequivalent to the RLD (see section 505(j) of the FD&C Act; compare section 505(j)(2)(C) for “petitioned ANDAs”). An applicant that can meet the requirements for approval under section 505(j) of the FD&C Act may rely upon the Agency’s finding of safety and effectiveness for the RLD and need not repeat the extensive nonclinical and clinical investigations required for approval of a “stand-alone” NDA submitted under section 505(b)(1) of the FD&C Act.

The timing of approval for a 505(b)(2) application and an ANDA (including a petitioned ANDA) is subject to certain patent and marketing exclusivity protections. An NDA applicant is required to submit information on any patent that claims the drug that is the subject of the NDA or that claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug (section 505(b)(1) and (c)(2) of the FD&C Act). Upon approval of an NDA under section 505(c) of the FD&C Act, we publish certain patent information provided by the NDA holder in the Orange Book, available electronically on FDA’s Web site at <http://www.fda.gov/cder>.

A 505(b)(2) application and ANDA must include an appropriate patent certification or statement for each patent that claims the listed drug(s) relied upon or RLD, respectively, or a method of using such drug and for which information is required to be filed under section 505(b)

or 505(c) of the FD&C Act. The 505(b)(2) or ANDA applicant must submit one or more of the following certifications or statements:

- That such patent information has not been filed (a paragraph I certification);
- that such patent has expired (a paragraph II certification);
- the date on which such patent will expire (a paragraph III certification);
- that such patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the 505(b)(2) application or ANDA is submitted (a paragraph IV certification);
- that there are no patents that claim the listed drug(s) or that claim a use of such drug (a “no relevant patents” statement, which is submitted instead of a patent certification); or
- that a method-of-use patent does not claim a use for which the 505(b)(2) or ANDA applicant is seeking approval (a 505(b)(2)(B) or (j)(2)(A)(viii) statement).

An applicant that submits a paragraph IV certification is required to give notice of the paragraph IV certification to the NDA holder for the listed drug(s) relied upon or RLD and each owner of the patent that is the subject of the certification. Notice of a paragraph IV certification subjects the 505(b)(2) or ANDA applicant to the risk that it will be sued for patent infringement. If the NDA holder or patent owner initiates a patent infringement action within 45 days after receiving notice of the paragraph IV certification, there generally will be a statutory 30-month stay of approval of the 505(b)(2) application or ANDA while the patent infringement litigation is pending (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act).

ANDA applicants have a statutory incentive to challenge listed patents that may be invalid, unenforceable, or not infringed by the drug product described in the ANDA. The first applicant to submit a substantially complete ANDA that contains, and for which the applicant



lawfully maintains, a paragraph IV certification may be eligible for a 180-day period of marketing exclusivity (180-day exclusivity) during which approval of subsequent ANDAs containing a paragraph IV certification to a listed patent for the same drug product will not be granted (see section 505(j)(5)(B)(iv) of the FD&C Act).

### III.A. History of This Rulemaking

On December 8, 2003, the MMA (Pub. L. 108-173) was signed into law. Title XI of the MMA significantly amended provisions of the FD&C Act that govern the approval of 505(b)(2) applications and ANDAs. Title XI of the MMA addressed two key concerns identified in an FTC report on “Generic Drug Entry Prior to Patent Expiration: An FTC Study” (July 2002) (Ref. 1) by limiting the availability of 30-month stays of approval on 505(b)(2) applications and ANDAs that are otherwise ready to be approved (30-month stays) and by establishing conditions under which a first applicant would forfeit the 180-day exclusivity period such that approval of subsequent ANDAs would no longer be blocked.

Section 1101 of the MMA provides that a 30-month stay of approval of a 505(b)(2) application or ANDA is available only if patent infringement litigation was initiated within the 45-day period after receipt of notice of a paragraph IV certification for a patent that had been submitted to FDA before the date of submission of the 505(b)(2) application or ANDA (excluding an amendment or supplement to the 505(b)(2) application or ANDA). The resulting incentive for an applicant to change the listed drug relied upon through an amendment of or a supplement to a 505(b)(2) application or ANDA is addressed by the MMA’s prohibition of the submission of certain types of changes (including those requiring reference to a different listed drug) in an amendment of or supplement to a 505(b)(2) application or ANDA. In addition,

section 1101 of the MMA amended the FD&C Act to specify certain types of court actions that will terminate a 30-month stay of approval.

Section 1101 of the MMA also created new requirements for 505(b)(2) and ANDA applicants sending notice of a paragraph IV certification, including changes to the timing and contents of such notice. In addition, the MMA established conditions under which a 505(b)(2) or ANDA applicant may bring a declaratory judgment action to obtain “patent certainty” (i.e., obtain a judicial determination of non-infringement, invalidity, or unenforceability) with respect to a listed patent for which it has given notice of a paragraph IV certification but has not been sued by the NDA holder or patent owner(s) within the statutory timeframe. If a patent infringement action is initiated against the 505(b)(2) or ANDA applicant, the MMA provides that the applicant may assert a counterclaim seeking an order requiring a correction or deletion of the patent information submitted to FDA for listing by the NDA holder.

Section 1102 of the MMA altered the conditions under which a 180-day period of marketing exclusivity attaches by requiring, among other things, that a first applicant lawfully maintain the paragraph IV certification contained in its submission of a substantially complete ANDA. In addition, section 1102 of the MMA established conditions under which a first applicant would forfeit the 180-day exclusivity period.

Section 1103 of the MMA clarified the types of bioavailability and bioequivalence data that can be used to support a 505(b)(2) application or ANDA for a drug that is not intended to be absorbed into the bloodstream.

On March 3, 2004, we published a notice in the Federal Register entitled “Generic Drug Issues; Request for Comments” (69 FR 9982), which invited public comment to further identify

issues related to the MMA provisions regarding 30-month stays, 180-day exclusivity, and bioavailability and bioequivalence, along with any suggestions for how to resolve those issues.

On February 6, 2015, we published a proposed rule to implement portions of the MMA that pertain to 30-month stays and other matters not related to forfeiture of 180-day exclusivity, and make our regulations governing 505(b)(2) applications and ANDAs consistent with the MMA's amendments to the FD&C Act (80 FR 6802, February 6, 2015; see also "Abbreviated New Drug Applications and 505(b)(2) Applications; Correction," 80 FR 13289, March 13, 2015). In addition, the proposed rule would amend the regulations in parts 314 and 320 (21 CFR parts 314 and 320) regarding 505(b)(2) applications and ANDAs to facilitate compliance with and efficient enforcement of the FD&C Act, and to clarify and update these regulations based on our practical experience implementing the provisions related to approval of 505(b)(2) applications and ANDAs. We will determine whether additional rulemaking related to 180-day exclusivity is necessary in the future.

FDA provided 120 days for public comment on the proposed rule, including a 30-day extension of the original comment period (see "Abbreviated New Drug Applications and 505(b)(2) Applications; Extension of Comment Period," 80 FR 22953, April 24, 2015). We received 13 comment letters on the proposed rule by the close of the comment period, each containing 1 or more comments on 1 or more issues. We received comments from pharmaceutical industry associations, brand and generic drug manufacturers, law firms, and a law student. Based on the comments received, FDA is finalizing the proposed rule with certain revisions and technical amendments.

### III.B. General Overview of the Final Rule

This final rule implements portions of Title XI of the MMA and revises and clarifies FDA regulations relating to 505(b)(2) applications and ANDAs. The final rule reflects our consideration of comments on the proposed rule, recent court decisions, and legislative enactments, and incorporates several clarifying revisions and technical amendments. Table 1 summarizes the substantive changes from the proposed rule to the final rule.

Table 1.--Highlights of Substantive Changes From the Proposed Rule to the Final Rule

21 CFR Section in Final Rule	Description of Change From Proposed Rule See comment or section of this document (identified in parentheses) for more detailed information regarding the change.
314.3	<p><i>Definitions (§ 314.3(b))</i></p> <ul style="list-style-type: none"> <li>Revises the definition of “505(b)(2) application” to clarify that it is an NDA for which “at least some of” the investigations relied upon by the applicant for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (see section V.P.3).</li> <li>Revises the definition of “acknowledgment letter” to delete the reference to 505(b)(2) applications and limit the applicability of this term to ANDAs (see section V.A.1).</li> <li>Revises the definition of “commercial marketing” to clarify that it includes the introduction or delivery for introduction into interstate commerce of the reference listed drug by the ANDA applicant (see section V.A.2).</li> <li>Revises the definition of “date of approval” to incorporate section 505(x) of the FD&amp;C Act (see section V.A.3).</li> <li>Revises the definition of “listed drug” to clarify that a drug product is deemed to be a listed drug on the “date of approval” of the NDA or ANDA (see section V.A.3).</li> <li>Revises the definition of “substantially complete application” to describe an ANDA that on its face is sufficiently complete to permit a substantive review and clarify that “sufficiently complete” means that the ANDA contains all the information required under section 505(j)(2)(A) of the FD&amp;C Act and does not contain a deficiency described in § 314.101(d) and (e) (see section V.A.5).</li> <li>Revises the definition of “tentative approval” to include a notification that an NDA or ANDA otherwise meets the requirements for approval under the FD&amp;C Act but cannot be approved because there is a period of exclusivity under section 505E of the FD&amp;C Act (see section V.A.7).</li> </ul>
314.50	<p><i>Patents claiming drug substance, drug product, or method of use (§ 314.50(i)(1)(i)(C))</i></p> <ul style="list-style-type: none"> <li>Clarifies that the requirement for a 505(b)(2) applicant to provide an appropriate patent certification or statement for each patent listed in the Orange Book for a pharmaceutically equivalent drug product applies to one such pharmaceutically equivalent drug product approved in an NDA before the date of submission of the original 505(b)(2) application and not a resubmission or a supplement (see section V.H).</li> </ul> <p><i>Method-of-use patent (§ 314.50(i)(1)(iii)(A))</i></p> <ul style="list-style-type: none"> <li>Clarifies that a 505(b)(2) applicant may submit a statement under section 505(b)(2)(B) of the FD&amp;C Act if the applicant is not seeking approval for “an” indication or other condition of use claimed by a method-of-use patent rather than “any” indications or other conditions of use claimed by the method-of-use patent (see section V.C.1).</li> </ul> <p><i>Untimely filing of patent information (§ 314.50(i)(4))</i></p> <ul style="list-style-type: none"> <li>Provides that an amendment to the description of the approved method(s) of use claimed by the patent will not be considered untimely filing of patent information if the amendment is submitted within 30 days of a decision by the USPTO or a Federal court that is specific to the patent and alters the construction of a method-of-use claim(s) of the patent, and the amendment contains a copy of the decision (see section V.B.2.b).</li> </ul>

Table 1.—Highlights of Substantive Changes From the Proposed Rule to the Final Rule—Continued

21 CFR Section in Final Rule	Description of Change From Proposed Rule See comment or section of this document (identified in parentheses) for more detailed information regarding the change.
314.52	<p><i>Sending the notice of paragraph IV certification (§ 314.52(b))</i></p> <ul style="list-style-type: none"> <li>Requires that a 505(b)(2) applicant send notice of a paragraph IV certification on or after the date of filing described in § 314.101(a)(2) or (3), but not later than 20 days after the date of the postmark on the “paragraph IV acknowledgment letter” (see section V.D.1.a).</li> <li>Removes the requirement for a 505(b)(2) applicant to submit an amendment at the time it sends notice of a paragraph IV certification and permits submission of a single amendment that contains all required information within 30 days of the date on which the last notice is received (see section V.D.3.b).</li> </ul> <p><i>Content of a notice of paragraph IV certification (§ 314.52(c))</i></p> <ul style="list-style-type: none"> <li>Omits the proposed requirement that notice of a paragraph IV certification must contain a statement that the 505(b)(2) applicant has received the paragraph IV acknowledgment letter (see section V.D.1.a).</li> </ul> <p><i>Amendment or supplement to a 505(b)(2) application (§ 314.52(d))</i></p> <ul style="list-style-type: none"> <li>Requires that after the date of filing of a 505(b)(2) application, the applicant must send notice of a paragraph IV certification included in an amendment or supplement at the same time that the amendment or supplement is submitted to FDA (see section V.D.1.b).</li> </ul>
314.53	<p><i>General requirements and Reporting Requirements (§ 314.53(b)(1) and (c)(2))</i></p> <ul style="list-style-type: none"> <li>Clarifies that if the method(s) of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, the NDA holder’s use code must describe only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product (see section V.B.1.c).</li> <li>Clarifies that the NDA holder submitting information on the method-of-use patent must identify with specificity the section(s) and subsection(s) of the approved labeling that describes the method(s) of use claimed by the patent submitted (see section V.B.1.c).</li> </ul> <p><i>Other Reporting Requirements (§ 314.53(c)(2))</i></p> <ul style="list-style-type: none"> <li>Omits the proposed requirement for an NDA holder to include information on whether a patent is a reissued patent of a patent previously submitted for listing (see section V.B.1.e).</li> <li>Maintains the current requirement for an NDA holder to include information on whether the patent has been submitted previously for the NDA (see section V.B.1.d).</li> <li>Adds the requirement for an NDA holder to identify, for a patent that has been submitted previously for listing, all change(s) from the previously submitted patent information and specify whether the change is related to the patent or related to an FDA action (see section V.B.2.b).</li> </ul> <p><i>Supplements (§ 314.53(d)(2))</i></p> <ul style="list-style-type: none"> <li>Omits the proposal to require an NDA holder to submit a statement with an NDA supplement if the NDA holder is not required to resubmit patent information pursuant to § 314.53(d)(2)(ii)(A) (see section V.B.2.a).</li> </ul>



Table 1.—Highlights of Substantive Changes From the Proposed Rule to the Final Rule—Continued

21 CFR Section in Final Rule	Description of Change From Proposed Rule See comment or section of this document (identified in parentheses) for more detailed information regarding the change.
314.53 (continued)	<p><i>Where to send submissions of Forms FDA 3542a and 3542 (§ 314.53(d)(4))</i></p> <ul style="list-style-type: none"> <li>Designates the CDER Central Document Room, rather than the OGD Document Room, as the official repository for submission of Form FDA 3542 and clarifies that Form FDA 3542 can be submitted electronically (see section V.B.2.c).</li> </ul> <p><i>Submission date of patent information (§ 314.53(d)(5))</i></p> <ul style="list-style-type: none"> <li>Establishes that the submission date of patent information is the earlier of the date on which Form FDA 3542 is date-stamped by the CDER Central Document Room or officially received by FDA in an electronic format submission that complies with § 314.50(l)(5) (see section V.B.2.d).</li> </ul> <p><i>Requests by persons other than the NDA holder (§ 314.53(f)(1))</i></p> <ul style="list-style-type: none"> <li>Requires that a person submitting a patent listing dispute for a method-of-use patent include a statement of dispute that is only a narrative description (no more than 250 words) of the person's interpretation of the scope of the patent (see section V.B.4.a).</li> <li>Requires that a person submitting a patent listing dispute directed to a drug substance, drug product, or method-of-use patent only include information in the statement of dispute for which the person consents to disclosure because FDA will send the text of the statement to the applicable NDA holder without review or redaction.</li> <li>Requires that the NDA holder's response to a patent listing dispute directed to a drug substance, drug product, or method-of-use patent include a signed verification of the accuracy and completeness of the response (see section V.B.4.a).</li> <li>Requires that the NDA holder's response to a patent listing dispute for a method-of-use patent also include a narrative description (no more than 250 words) of the NDA holder's interpretation of the scope of the patent that explains why the existing or amended "use code" describes only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Requires that the narrative description only contain information for which the NDA holder consents to disclosure because FDA will send the text of the statement to the person who submitted the patent listing dispute without review or redaction (see section V.B.4.a).</li> <li>Provides that FDA will promptly post information on its Web site regarding whether a patent listing dispute has been submitted for a published description of a patented method of use for a drug product and whether the NDA holder has timely responded to the patent listing dispute (see section V.B.4.a).</li> <li>Omits the proposal to review a proposed labeling carve-out with deference to the 505(b)(2) and/or ANDA applicant(s)' interpretation of the scope of the patent in certain circumstances, which is not being finalized at this time (see section V.B.4.a).</li> </ul>
314.54	<p><i>Procedures for submission of a 505(b)(2) application requiring investigations for approval of a new indication for, or other change from, a listed drug (§ 314.54(a)(1))</i></p> <ul style="list-style-type: none"> <li>Clarifies that the requirement for a 505(b)(2) applicant to identify one pharmaceutically equivalent drug product approved in an NDA as a listed drug (or an additional listed drug) relied upon applies before the date of submission of the original 505(b)(2) application and not a resubmission or a supplement (see section V.H).</li> </ul>

Table 1.--Highlights of Substantive Changes From the Proposed Rule to the Final Rule--Continued

21 CFR Section in Final Rule	Description of Change From Proposed Rule See comment or section of this document (identified in parentheses) for more detailed information regarding the change.
314.60	<p><i>Patent certification requirements (§ 314.60(f))</i></p> <ul style="list-style-type: none"> <li>Requires that if an amendment to the 505(b)(2) application does not contain a patent certification or statement, the applicant must verify that the proposed change described in the amendment is not: (1) A new indication or other condition of use; (2) a new strength; (3) an other-than-minor change in product formulation; or (4) a change to the physical form or crystalline structure of the active ingredient (see section V.F.1).</li> </ul>
314.70	<p><i>Patent certification requirements (§ 314.70(i))</i></p> <ul style="list-style-type: none"> <li>Omits proposed § 314.70(i) on patent certification requirements for 505(b)(2) supplements, which is not being finalized at this time (see section V.F.2).</li> </ul>
314.90	<p><i>Waivers (§ 314.90)</i></p> <ul style="list-style-type: none"> <li>No substantive changes from the proposed rule (see section V.L).</li> </ul>
314.93	<p><i>Petition to request a change from a listed drug (§ 314.93)</i></p> <ul style="list-style-type: none"> <li>No substantive changes from the proposed rule (see section V.I).</li> </ul>
314.94	<p><i>Method-of-use patent (§ 314.94(a)(12)(iii)(A))</i></p> <ul style="list-style-type: none"> <li>Clarifies that an ANDA applicant may submit a statement under section 505(j)(2)(A)(viii) of the FD&amp;C Act if the applicant is not seeking approval for “an” indication or other condition of use claimed by a method-of-use patent rather than “any” indications or other conditions of use claimed by the method-of-use patent (see section V.C.1).</li> </ul> <p><i>Untimely filing of patent information (§ 314.94(a)(12)(vi))</i></p> <ul style="list-style-type: none"> <li>Provides that an amendment to the description of the approved method(s) of use claimed by the patent will not be considered untimely filing of patent information if the amendment is submitted within 30 days of a decision by the USPTO or a Federal court that is specific to the patent and alters the construction of a method-of-use claim(s) of the patent, and the amendment contains a copy of the decision (see section V.B.2.b).</li> </ul> <p><i>After request to remove a patent or patent information from the list (§ 314.94(a)(12)(viii)(B))</i></p> <ul style="list-style-type: none"> <li>Omits the proposed requirement for a first applicant to lawfully maintain a paragraph IV certification to an original patent that has been reissued, which is not being finalized (see section V.B.1.e and V.E.3).</li> </ul>
314.95	<p><i>Sending the notice of paragraph IV certification (§ 314.95(b))</i></p> <ul style="list-style-type: none"> <li>Deletes the reference to an “acknowledgment letter” in § 314.95(b)(1) and (b)(2) because an ANDA applicant will now receive a “paragraph IV acknowledgment letter” if the ANDA contains a paragraph IV certification before the ANDA is received (see section V.D.1.a).</li> <li>Removes the requirement for an ANDA applicant to submit an amendment at the time it sends notice of a paragraph IV certification and permits submission of a single amendment that contains all required information within 30 days of the date on which the last notice is received (see section V.D.3.b).</li> </ul>



Table 1.--Highlights of Substantive Changes From the Proposed Rule to the Final Rule--Continued

21 CFR Section in Final Rule	Description of Change From Proposed Rule See comment or section of this document (identified in parentheses) for more detailed information regarding the change.
314.96	<p><i>Patent certification requirements (§ 314.96(d))</i></p> <ul style="list-style-type: none"> <li>Clarifies that a paragraph IV certification to a patent or patent claim for which an ANDA applicant previously submitted a paragraph IV certification is a “recertification” rather than an “amendment” of the paragraph IV certification (see section V.F.3).</li> <li>Requires that if an amendment to the ANDA does not contain a patent certification or statement, the applicant must verify that the proposed change described in the amendment is not: (1) a new indication or other condition of use; (2) a new strength; (3) an other-than-minor change in product formulation; or (4) a change to the physical form or crystalline structure of the active ingredient (see section V.F.1).</li> </ul>
314.97	<p><i>Patent certification requirements (§ 314.97(c))</i></p> <ul style="list-style-type: none"> <li>Omits proposed § 314.97(c) on patent certification requirements for ANDA supplements, which is not being finalized at this time (see section V.F.2).</li> </ul>
314.99	<p><i>Other responsibilities of an applicant of an ANDA (§ 314.99)</i></p> <ul style="list-style-type: none"> <li>No substantive changes from the proposed rule (see section V.L).</li> </ul>
314.101	<p><i>Receiving an ANDA (§ 314.101(b))</i></p> <ul style="list-style-type: none"> <li>Clarifies current Agency practice that following a refuse-to-accept decision, an ANDA applicant may: Withdraw the ANDA under § 314.99; correct the deficiencies and resubmit the ANDA; or take no action, in which case FDA may consider the ANDA withdrawn after 1 year (see section V.J.2).</li> <li>Omits the proposed administrative consequence for ANDA applicants who fail to send notice of paragraph IV certification within the statutory timeframe (see section V.J.3).</li> </ul> <p><i>NDA or ANDA deficiencies (§ 314.101(d))</i></p> <ul style="list-style-type: none"> <li>Clarifies that FDA will consider the nature (e.g., major or minor) of the deficiencies, including the number of deficiencies in the ANDA in determining whether an ANDA is incomplete on its face (see section V.J.2).</li> </ul> <p><i>Regulatory Deficiencies (§ 314.101(e))</i></p> <ul style="list-style-type: none"> <li>Clarifies that FDA will refuse to file a 505(b)(2) application or refuse to receive an ANDA if submission is not permitted under sections 505(c)(3)(E)(ii), 505(j)(5)(F)(ii), 505A(b)(1)(A)(i)(I), 505A(c)(1)(A)(i)(I), or 505E(a) of the FD&amp;C Act (see section V.A.7).</li> </ul>
314.105	<p><i>Approval of an NDA and an ANDA (§ 314.105)</i></p> <ul style="list-style-type: none"> <li>Removes the proposed statement that an NDA is approved on the date of the issuance of the approval letter, and clarifies that a new drug product may not be marketed until the “date of approval,” rather than the “date of the approval letter” (see section V.A.3).</li> <li>Clarifies that approval of a 505(b)(2) application or ANDA also may be delayed by a period of exclusivity for the listed drug under section 505E of the FD&amp;C Act (see section V.A.7).</li> </ul>

Table 1.--Highlights of Substantive Changes From the Proposed Rule to the Final Rule--Continued

21 CFR Section in Final Rule	Description of Change From Proposed Rule See comment or section of this document (identified in parentheses) for more detailed information regarding the change.
314.107	<p><i>Disposition of patent litigation (§ 314.107(b)(3))</i></p> <ul style="list-style-type: none"> <li>Revises § 314.107(b)(3)(v) to more clearly describe the timing of approval of a 505(b)(2) application or ANDA when a preliminary injunction is entered by a Federal district court before the expiration of a 30-month stay (or 7½ years where applicable) (see section V.M.2.g).</li> <li>Clarifies that the 30-month period (or 7½ years where applicable) will be terminated if the court(s) enter(s) an order of dismissal without a finding of infringement in each pending suit for patent infringement brought within 45 days of receipt of the notice of paragraph IV certification sent by the 505(b)(2) or ANDA applicant (see section V.M.2.j).</li> </ul> <p><i>Delay due to exclusivity (§ 314.107(d))</i></p> <ul style="list-style-type: none"> <li>Clarifies that approval of a 505(b)(2) application or ANDA also may be delayed by a period of exclusivity for the listed drug under section 505E of the FD&amp;C Act (see section V.M.4).</li> </ul> <p><i>Notification of court actions or written consent to approval (§ 314.107(e))</i></p> <ul style="list-style-type: none"> <li>Requires submission of a copy of any “written consent to approval” by the patent owner or exclusive patent licensee, rather than any “documented agreement,” and clarifies that a copy of any order entered by the court terminating the 30-month or 7½-year period includes an order described in § 314.107(b)(3)(vii) and (viii) (see section V.M.5).</li> <li>Provides that all information required by § 314.107(e)(1) must be sent to the applicant’s NDA or ANDA rather than to OGD or the appropriate division in OND (see section V.M.5).</li> </ul>
314.108	<p><i>New drug product exclusivity (§ 314.108)</i></p> <ul style="list-style-type: none"> <li>No substantive changes from the proposed rule.</li> </ul>
314.125	<p><i>Refusal to approve an NDA (§ 314.125)</i></p> <ul style="list-style-type: none"> <li>Clarifies that FDA may refuse to approve a 505(b)(2) application if it does not contain a patent certification or statement with respect to each listed patent for a drug product approved in an NDA that is pharmaceutically equivalent to the drug product for which the original 505(b)(2) application is submitted and that was approved before the original 505(b)(2) application was submitted (see section V.H).</li> </ul>
314.127	<p><i>Refusal to approve an ANDA (§ 314.127)</i></p> <ul style="list-style-type: none"> <li>No substantive changes from the proposed rule (see section V.L).</li> </ul>
320.1	<p><i>Definitions (§ 320.1)</i></p> <ul style="list-style-type: none"> <li>No substantive changes from the proposed rule (see section V.A).</li> </ul>
320.23	<p><i>Basis for measuring in vivo bioavailability or demonstrating bioequivalence (§ 320.23)</i></p> <ul style="list-style-type: none"> <li>No substantive changes from the proposed rule (see section V.N).</li> </ul>

#### IV. Legal Authority

The MMA and sections 505, 505A, 505E, 527, and 701 (21 U.S.C. 355, 355a, 355f, 360cc, and 371) of the FD&C Act provide the principal legal authority for this final rule.

Section 505(b) of the FD&C Act describes the contents of an NDA, including a 505(b)(2) application, and describes patent listing and patent certification requirements for NDAs. Section 505(j) of the FD&C Act describes the contents of an ANDA, including bioequivalence information, patent certification requirements, and criteria for a petitioned ANDA. Section 505(b) and (j) of the FD&C Act restrict certain amendments and supplements to a 505(b)(2) application or an ANDA. Section 505(b), (c), and (j) of the FD&C Act describe the timing of approval for 505(b)(2) applications and ANDAs that are subject to certain patent and marketing exclusivity protections. Section 505(j) also describes the availability of 180-day exclusivity for a first applicant. Section 505(x) describes the date of approval of an NDA for which FDA intends to recommend controls under the Controlled Substances Act (CSA). Section 701(a) of the FD&C Act provides FDA with the authority to issue regulations for the efficient enforcement of the FD&C Act.

Section 505A of the FD&C Act describes the availability of pediatric exclusivity and describes the effect of such exclusivity on approval of 505(b)(2) applications and ANDAs. Section 505E of the FD&C Act describes the availability of an exclusivity period extension for certain designated qualified infectious disease products. Section 527 of the FD&C Act describes the effect of orphan exclusivity on approval of 505(b)(2) applications and ANDAs.

Thus, sections 505, 505A, 505E, and 527 of the FD&C Act, in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act, serve as our principal legal authority for this final rule.

#### V. Comments on the Proposed Rule and FDA Response

We received 13 comment letters on the proposed rule by the close of the comment period, each containing 1 or more comments on 1 or more issues. We received comments from

pharmaceutical industry associations, brand and generic drug manufacturers, law firms, and a law student. Several comments made general remarks supporting the proposed rule without focusing on a particular proposed provision.

We describe and respond to specific comments in sections V.A through V.O. We have numbered each comment to help distinguish between different comments. We have grouped similar comments together under the same number, and, in some cases, we have separated different issues discussed in the same comment and designated them as distinct comments for purposes of our responses. The number assigned to each comment or comment topic is purely for organizational purposes and does not signify the comment's value or importance or the order in which comments were received. We also received comments on topics related to 505(b)(2) applications and ANDAs that are outside the scope of the proposed rule, including, for example, issues related to forfeiture of eligibility for 180-day exclusivity and the Drug Efficacy Study Implementation, and we are not addressing these comments at this time. We are currently implementing the 180-day exclusivity provisions of the MMA directly from the statute and will determine whether additional rulemaking is necessary in the future.

#### V.A. Definitions (§ 314.3(b))

We proposed to amend § 314.3(b) to define terms relevant to amendments to the FD&C Act made by the MMA and to add definitions of terms that have been used by the Agency in the context of implementing section 505(b) and (j) of the FD&C Act. We also proposed amendments to § 314.3(b) to conform with other changes in the proposed rule (80 FR 6802), and to incorporate new definitions. We received a general comment expressing support for FDA's efforts to clarify and update various definitions that are necessary for the efficient enforcement of the Hatch-Waxman Amendments. We received no comments on our proposed definitions of

“180-day exclusivity period,” “abbreviated new drug application or ANDA,” “active ingredient,” “ANDA holder,” “component,” “inactive ingredient,” “NDA holder,” “new drug application or NDA,” “original NDA,” “paragraph IV certification,” “patent owner,” “reference standard,” “strength,” and “therapeutic equivalents.” We also received no comments on our proposed revisions to the current definitions of “abbreviated application,” “act,” “applicant,” “application,” “listed drug,” and “the list.” In addition, we received no comments on our proposed relocation of the definition of “active moiety” that currently is in § 314.108(a) to § 314.3(b). Finally, we received no comments on our proposed relocation of the definitions that currently are in § 320.1(a) and (c) through (g) to § 314.3(b), our proposed deletion of § 320.1(b), and our proposed revisions to the definitions of “bioavailability” and “bioequivalence.” Therefore, we are finalizing these definitions without change, except for the technical amendment to the definition of “listed drug” described in section V.A.3 (Response 4) and the technical amendments to the definitions of “original NDA,” “resubmission,” and “therapeutic equivalents” described in section V.P.1. We also describe a technical amendment to the definition of “505(b)(2) application” in section V.P.3 and the addition of the defined term “Agency” in section V.P.1.

#### V.A.1. Definitions of “Acknowledgment Letter” and “Paragraph IV Acknowledgment Letter”

We proposed to establish a definition of the term “paragraph IV acknowledgment letter” and the related term “acknowledgment letter” to facilitate implementation of the MMA’s requirement for a 505(b)(2) or ANDA applicant to send notice of a paragraph IV certification within 20 days after the date of the postmark on the notice with which FDA informs the applicant that the application has been filed (see section 505(b)(3)(B)(i) and (j)(2)(B)(ii)(I) of the FD&C Act and section V.A.6). We proposed to define “paragraph IV acknowledgment letter” to

mean a written, postmarked communication from FDA to an applicant stating that the Agency has determined that a 505(b)(2) application or ANDA containing a paragraph IV certification is sufficiently complete to permit a substantive review. For 505(b)(2) applications and ANDAs that do not contain a paragraph IV certification, we proposed to define “acknowledgment letter” to mean a written, postmarked communication from FDA to an applicant stating that the Agency has determined that a 505(b)(2) application or ANDA is sufficiently complete to permit a substantive review. The proposed “acknowledgment letter” or “paragraph IV acknowledgment letter” would indicate that the 505(b)(2) application is regarded as filed or the ANDA is regarded as received (see proposed § 314.3(b)).

As explained in the proposed rule, the “paragraph IV acknowledgment letter” for 505(b)(2) applications that rely on the Agency’s finding of safety and/or effectiveness for a listed drug and contain a paragraph IV certification would be the filing communication that generally is sent to the 505(b)(2) applicant not later than 14 calendar days after the 60-day filing date and sometimes is referred to as the “74-day letter” (see 80 FR 6802 at 6811 and 6814 to 6815). Unlike the paragraph IV acknowledgment letter for ANDAs, the filing communication is typically sent by the Office of New Drugs (OND) in the Center for Drug Evaluation and Research (CDER) in a franked envelope that may not bear a postmark made by the U.S. Postal Service (USPS). For purposes of § 314.52(b) and (c) only, we proposed that the “date of the postmark” on the “paragraph IV acknowledgment letter” would be considered to be four calendar days after the date on which the filing communication is signed by the signatory authority (generally the Division Director or designee in the OND review division), which generally reflects the date on which the document is received by the USPS (see definition of “postmark” in proposed § 314.3). In the proposed rule, we explained that if OND were to send

the filing communication via electronic transmission in the future, then our proposed definition of a “postmark” that documents an electronic event would apply (see proposed § 314.3(b) and section V.A.6).

In the following paragraphs, we discuss a comment on these proposed definitions. We also received a comment that agrees with the proposed definition of “paragraph IV acknowledgment letter” and the inclusion of this term in revised § 314.101(b)(2). After considering these comments, we are revising the definition of “acknowledgment letter” to delete the reference to 505(b)(2) applications, thereby limiting the applicability of this term to ANDAs. We are finalizing the definition of “paragraph IV acknowledgment letter” without change.

(Comment 1) One comment requests that FDA clarify whether the terms “acknowledgment letter,” “acceptance for filing letter,” and “paragraph IV acknowledgment letter” can be used interchangeably to refer to the letter sent to applicants for ANDAs that contain a paragraph IV certification.

(Response 1) FDA separately defines the terms “acknowledgment letter” and “paragraph IV acknowledgment letter” for ANDAs because the “paragraph IV acknowledgment letter” contains information on certain regulatory requirements associated with a paragraph IV certification. For administrative reasons, it had been FDA’s practice to send an “acknowledgment letter” rather than a “paragraph IV acknowledgment letter” to an ANDA applicant if an original ANDA contained a patent certification or statement other than a paragraph IV certification, and the applicant submitted an amendment containing a paragraph IV certification before the ANDA has been received for substantive review. Accordingly, we proposed to use both terms in the regulations where appropriate (see proposed § 314.95). Upon further consideration, we are modifying our administrative practices to send a “paragraph IV



acknowledgment letter” to an ANDA applicant if the ANDA contains a paragraph IV certification at any time prior to receipt of the ANDA. We are making conforming revisions to § 314.95(b)(1) and (2), (c)(3), and (d)(2) to remove the reference to an “acknowledgment letter.” We are retaining a revised definition of the term “acknowledgment letter” in § 314.3(b) because FDA’s Office of Generic Drugs (OGD) will continue to send “acknowledgment letters” for ANDAs that do not contain a paragraph IV certification at the time of receipt (see, e.g., section V.D.1.b). (The defined term “acknowledgment letter” for ANDAs differs from the informal use of this term for NDAs, which acknowledges the submission of an NDA before the Agency has determined whether the NDA can be filed.) FDA no longer uses the term “acceptance for filing letter,” which is an informal term that previously was used to describe an acknowledgment letter for an ANDA.

FDA has concluded that that it is unnecessary to distinguish between an “acknowledgment letter” and a “paragraph IV acknowledgment letter” for a 505(b)(2) application. If the 505(b)(2) application contains a paragraph IV certification at any time before the 505(b)(2) application is filed, the filing communication that FDA sends to NDA applicants also will be the “paragraph IV acknowledgment letter” for 505(b)(2) applicants for purposes of determining the date by which notice of paragraph IV certification must be sent (see § 314.52). We are making a conforming revision to § 314.52(d) to remove the reference to an “acknowledgment letter” (see section V.D.1.b).

#### V.A.2. Definition of “Commercial Marketing”

We proposed to define “commercial marketing” to mean the introduction or delivery for introduction into interstate commerce of a drug product described in an approved ANDA, outside the control of the ANDA holder, except for investigational use under part 312 of this chapter (21



CFR part 312), but that does not include transfer of the drug product for reasons other than sale to parties identified in the approved ANDA (see proposed § 314.3(b)). In the following paragraphs, we discuss three comments on this proposed definition. After considering these comments, we are making editorial corrections to clarify the types of transfers of the drug product for reasons other than sale that fall within the exception to commercial marketing. We also are making amendments to clarify that the definition of commercial marketing includes the introduction or delivery for introduction into interstate commerce of the reference listed drug by the ANDA applicant.

(Comment 2) One comment recommends clarifying that commercial marketing does not include transfer of the drug product to a third-party logistics provider or contractor who is not identified in the ANDA, provided that the transfer does not take the drug product outside the control of the ANDA holder (e.g., transfer of the drug product for storage or further distribution only as the ANDA holder may direct in the future). This comment also suggests revising the structure of the definition to improve clarity. Another comment maintains that the proposed definition would limit business flexibility, given that an ANDA applicant's transfer of the drug product to a re-packager (e.g., to facilitate packaging validation or preparation for product launch) would be considered commercial marketing because re-packagers are not identified in ANDAs.

(Response 2) FDA declines to expand the exception to commercial marketing to include transfer of the drug product, outside the control of the ANDA applicant, for reasons other than sale to third parties not identified in the ANDA. FDA's amended definition of "commercial marketing" creates a bright-line rule for establishing the date of first commercial marketing of the drug by any first applicant for purposes of determining the start of the 180-day exclusivity

period (see section 505(j)(5)(B)(iv)(I) of the FD&C Act and § 314.107(c)(2)). The amended definition also facilitates implementation of the statutory provision by which a first applicant may forfeit eligibility for 180-day exclusivity due to failure to market the drug by the timeframe described in the statute (see section 505(j)(5)(D)(i)(I) of the FD&C Act).

Under the amended definition in § 314.3(b), “commercial marketing” of the drug product refers to a transfer of the drug product outside the control of the ANDA applicant, subject to specified exceptions, and thus does not include a transfer of the drug product within the control of the ANDA applicant. As we explained in the proposed rule, the amended definition is intended to clarify that the ANDA applicant’s shipment of a drug product described in an ANDA to any party named in the ANDA for purposes described in the ANDA (e.g., contract packaging) is not “commercial marketing” of the drug product even though such transfer arguably places the drug products outside of the control of the manufacturer for some period of time (80 FR 6802 at 6812). Among other things, an ANDA holder would be required to identify a packager or re-packager in a supplement to the ANDA if different equipment or facilities are used that have a moderate potential to have an adverse effect on factors that may relate to the safety and effectiveness of the drug product (see 21 U.S.C. 356a and § 314.70(c); compare § 314.70(d)). We also note that storage and distribution facilities often are identified in ANDAs (see, e.g., draft guidance for industry entitled “Pre-Launch Activities Importation Requests (PLAIR)” (July 2013) at 3, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>). Accordingly, we do not expect the amended definition to have a significant impact on ANDA applicants’ business arrangements with third parties.

FDA agrees that the definition of “commercial marketing” should be revised further for clarity. We also are making amendments to remove the reference to an “approved” ANDA and to further clarify that the definition of commercial marketing includes an ANDA applicant’s commercial marketing of the reference listed drug, including an authorized generic drug (see section 505(j)(5)(B)(iv)(I) of the FD&C Act). As revised, commercial marketing is the introduction or delivery for introduction into interstate commerce of a drug product described in an ANDA, outside the control of the ANDA applicant, except that the term does not include transfer of the drug product for investigational use under part 312 of this chapter or transfer of the drug product to parties identified in the ANDA for reasons other than sale. Commercial marketing includes the introduction or delivery for introduction into interstate commerce of the reference listed drug by the ANDA applicant.

(Comment 3) One comment agrees with the proposed definition of “commercial marketing” but recommends specifically excluding charitable donations of drug product.

(Response 3) FDA disagrees with the recommendation to exclude charitable donations of drug product from the definition of “commercial marketing.” A drug product is introduced or delivered for introduction into interstate commerce, outside the control of the ANDA applicant, when an ANDA applicant donates the drug product to a charitable institution or organization (e.g., a nonprofit hospital or health care entity). This introduction or delivery for introduction into interstate commerce subjects the donated drug product to applicable statutory and regulatory requirements, including, but not limited to, requirements intended to ensure that the drug product is not adulterated or misbranded (see, e.g., 21 U.S.C. 331, 351, and 352). Moreover, even if the charitable institution or organization is identified in the ANDA, a charitable donation of drug product is not necessarily a transfer of the drug product for reasons other than sale, given that

there are circumstances in which a donated drug product may be sold (see 21 U.S.C. 353(c)(3)(B) and 21 CFR 203.22). FDA does not believe the definition of “commercial marketing” will impact charitable donation of drug product, given that charitable donation of drug product met the criteria for commercial marketing under the previous definition in § 314.107(c)(4). The comment does not provide any explanation for the proposed change, and we do not believe that the proposed change is necessary.

#### V.A.3. Definition of “Date of Approval”

We proposed to move the definition of “date of approval” from § 314.108(a) to § 314.3(b) with several revisions. We proposed that the date of approval would mean the date on the approval letter from FDA stating that the NDA or ANDA is approved (see proposed § 314.3(b)). Our proposed revisions broadened the definition to include the date of approval for an ANDA, and incorporated the defined term “approval letter.” We also proposed to remove the caveat that the date of approval is the date on the approval letter whether or not final printed labeling or other materials must still be submitted as long as approval of such labeling or materials is not expressly required.

In the following paragraphs, we discuss two comments that disagree with these proposed changes. After these comments were submitted, Congress enacted the Improving Regulatory Transparency for New Medical Therapies Act (IRTNMTA) (Pub. L. 114-89), which addresses the primary concern expressed by comments regarding the proposed revision to the definition. We are finalizing the definition with technical amendments to incorporate IRTNMTA.

(Comment 4) Two comments recommend that FDA retain the former definition of “date of approval” in § 314.108 because the definition addresses circumstances in which the date on the approval letter for an NDA is not the same as the date on which an applicable exclusivity

period begins to run. The comments contend that the qualifying phrase “as long as approval of such [final printed] labeling or materials is not expressly required” in the former definition of “date of approval” is not reflected elsewhere in the Agency’s regulations. Moreover, the comments assert that the proposed revision to the definition would effectively reduce the exclusivity period for certain approved drug products that cannot be commercially marketed until the Drug Enforcement Administration (DEA) has scheduled the drug as a controlled substance or until FDA has approved a proprietary name (where the name is necessary for the safe use of the drug). The comments maintain that FDA did not clearly describe and invite comment on these effects of the proposed revision to the definition.

(Response 4) We disagree with comments recommending that we retain the former definition of “date of approval” in § 314.108. As we explained in the proposed rule, FDA’s regulations in § 314.105(b) specifically address the circumstances in which FDA will approve an NDA and issue the applicant an approval letter on the basis of draft labeling. Since publication of the proposed rule, FDA has determined that an ANDA also may be approved on the basis of draft labeling, provided that the only deficiencies in the draft labeling are editorial or similarly minor in nature (see guidance for industry entitled “Acceptability of Draft Labeling to Support ANDA Approval” (October 2015), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>) (superseding FDA’s former policy that final printed labeling is required for approval of an ANDA). If draft labeling deficiencies have not yet been resolved and are more than “editorial or similar minor deficiencies,” then the appropriate action is a complete response letter (see §§ 314.125(b) and 314.110). In the exceptional circumstances in which FDA has not yet approved a proprietary name for a proposed drug product and determines that the product cannot

be marketed without a proprietary name, the applicant should receive a complete response letter (compare Letter from Janet Woodcock, M.D., Director, CDER, to Anil Hiteshi, Spectrum Pharmaceuticals, Inc., dated February 24, 2015, regarding Docket No. FDA-2014-P-1615, available at <http://www.regulations.gov>) (denying request for revision of the approval date because the approval letter expressly stated that Spectrum could market the product with labeling bearing only the established name until a proprietary name could be agreed upon). Accordingly, it is unnecessary to address any requirements for approval of final printed labeling in the definition of “date of approval.”

On November 25, 2015, Congress enacted IRTNMTA, which addresses concerns that delays in scheduling a newly approved drug may reduce an applicable exclusivity period that commences on the “date of approval.” IRTNMTA provides that the date of approval for an NDA for which FDA intends to recommend controls under the CSA is the later of the date an NDA is approved under section 505(c) of the FD&C Act or the date of issuance of the interim final rule controlling the drug (see section 505(x)(1) and (2) of the FD&C Act). To incorporate IRTNMTA, we are revising the definition of “date of approval” to mean the date on the approval letter from FDA stating that the NDA or ANDA is approved, except that the date of approval for an NDA described in section 505(x)(1) of the FD&C Act is determined as described in section 505(x)(2) of the FD&C Act (see § 314.3(b)).

As reflected in the revised definition, we are currently implementing IRTNMTA directly from the statute and will determine whether additional rulemaking is necessary in the future. However, given the broader relevance of the term “date of approval” to matters covered in part 314, we are making other technical amendments to align with the revised definition and enhance clarity. These technical amendments are described in the following paragraphs.

We are further revising the proposed definition of “listed drug” to establish that a drug product is deemed to be a listed drug on the “date of approval” for the NDA or ANDA for that drug product, rather than on the “date of the approval letter” (see § 314.3(b)). This technical amendment clarifies the listed drug status of a drug product described in section 505(x)(1) of the FD&C Act, and the corresponding date on which the drug product will be identified in the Orange Book (the list) as a listed drug. We are revising § 314.105(a) to remove the proposed statement that an NDA is approved on the date of the issuance of the approval letter. This statement may be inaccurate with respect to drug products described in section 505(x)(1) of the FD&C Act, and the text is unnecessary in light of the revised definition of “date of approval” (see § 314.3(b)). We also are revising § 314.105(a) to state that a new drug product may not be marketed until the date of approval, rather than the date of the approval letter, for consistency with IRTNMTA. Although section 505(x)(1) of the FD&C Act does not apply to ANDAs, we are making the same revisions to § 314.105(d) for consistency. In addition, we are revising § 314.107(b) to clarify that this provision describes how to determine the first possible date on which a 505(b)(2) application or ANDA can be approved, rather than the “date of approval.” We also are replacing the phrase “the date the patented drug was approved” with “the date of approval” in § 314.107(b)(3)(i)(B) to incorporate the revised definition. Finally, in the paragraph heading for § 314.108(b), we are replacing the phrase “date of approval” with “timing of approval” to more accurately characterize the content of this paragraph.

In the sections of parts 314 and 320 that are the subject of this rulemaking, the references to the “date of approval” are intended to refer to the revised definition in § 314.3(b). For example, we are maintaining the reference to “date of approval” in § 314.53(c)(2)(ii) to ensure that there is no ambiguity post-IRTNMTA about the required timeframe for submission of patent

information after approval, given the implications of untimely filing of patent information on the patent certification obligations of 505(b)(2) applicants and ANDA applicants that rely upon the listed drug (see §§ 314.50(i)(4) and 314.94(a)(12)(vi)). Accordingly, for an NDA subject to IRTNMTA, the NDA holder must submit Form FDA 3542 within 30 days of the later of the date on which the NDA is approved under section 505(c) of the FD&C Act or the date of issuance of the interim final rule controlling the drug for the patent information to be considered timely filed.

#### V.A.4. Definition of “Dosage Form”

We proposed to define “dosage form” to mean the physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product. The physical manifestation includes such factors as: (1) The physical appearance of the drug product, (2) the physical form of the drug product prior to dispensing to the patient, (3) the way the product is administered, and (4) design features that affect frequency of dosing (see proposed § 314.3(b)). In the following paragraphs, we discuss a comment on this proposed definition. After considering this comment, we are finalizing the definition without change.

(Comment 5) One comment recommends that FDA broaden the definition of “dosage form” by including an additional factor to describe the physical manifestation of a drug product. The comment requests that FDA establish that a drug product with features that impart properties designed to deter tampering, abuse, or misuse of the drug product does not have the same dosage form as a similar version of the drug product that does not have such properties. The comment suggests that this would clarify that abuse-deterrent formulations and non-abuse-deterrent formulations of a drug product cannot be considered pharmaceutical equivalents or therapeutic equivalents.



(Response 5) FDA declines to adopt the comment’s suggestion at this time. FDA may address issues related to the pharmaceutical equivalence and therapeutic equivalence of abuse-deterrent formulations of a drug product through rulemaking or other regulatory mechanisms.

#### V.A.5. Definitions of “First Applicant” and “Substantially Complete Application”

We proposed to define the terms “first applicant” and “substantially complete application” to incorporate into our regulations the definitions established by the MMA, with minor editorial changes and additional clarifying text (see section 505(j)(5)(B)(iv)(II)(bb) and (cc) of the FD&C Act). We proposed to define “first applicant” to mean an applicant that, on the first day on which a substantially complete ANDA containing a paragraph IV certification is submitted for approval of a drug, submits a substantially complete ANDA that contains, and for which the applicant lawfully maintains, a paragraph IV certification for the drug (see proposed § 314.3(b)). We proposed to delete the definition of “applicant submitting the first application” in former § 314.107(c)(2) because that definition was superseded by the statutory definition.

We also proposed to define “substantially complete application” to mean an ANDA that on its face is sufficiently complete to permit a substantive review and contains all the information required under section 505(j)(2)(A) of the FD&C Act and § 314.94 (see proposed § 314.3(b)). We clarified that any information referenced in the ANDA must have been provided to FDA for the ANDA to be substantially complete, and we provided examples of other bases for finding that an ANDA is not substantially complete (see 80 FR 6802 at 6816 to 6817).

In the following paragraphs, we discuss a comment on these proposed definitions. After considering this comment, we are revising the definition of “substantially complete application” for consistency with § 314.101 and making an editorial correction for clarity. We are finalizing

the definition of “first applicant” with editorial changes to more clearly incorporate the defined term “substantially complete application.”

(Comment 6) One comment recommends that FDA revise the definitions of “first applicant” and “substantially complete application” to clarify the content required to support a decision that an ANDA is substantially complete “on its face” in order to distinguish deficiencies that may preclude receipt of an ANDA from review issues.

(Response 6) FDA is revising the definition of “substantially complete application” for consistency with other regulations outlining the required content of an ANDA and to enhance clarity. Under existing § 314.101(b), FDA will receive an ANDA if FDA finds that none of the reasons in § 314.101(d) and (e) applies for considering the ANDA not to have been received. The deficiencies described in § 314.101(d) that may result in refusal to receive an ANDA include, but are not limited to, an ANDA that is incomplete “because it does not on its face contain information required” under section 505(j) of the FD&C Act and § 314.94 (see § 314.101(d)(3)).

We are revising the definition of “substantially complete application” to include an express definition of “sufficiently complete” to permit a substantive review that aligns with our standard for receiving an ANDA. As revised, a “substantially complete application” is an ANDA that on its face is sufficiently complete to permit a substantive review. “Sufficiently complete” to permit a substantive review means that the ANDA contains all the information required under section 505(j)(2)(A)(i) through (viii) of the FD&C Act and does not contain a deficiency described in § 314.101(d) and (e) (see § 314.3(b)). The phrase “on its face” describes FDA’s threshold determination that the ANDA includes the information required to make it sufficiently complete to permit a substantive review (i.e., information corresponding to the

statutory and regulatory requirements for an ANDA). This evaluation does not involve a substantive review of the data in the ANDA (see § 314.101(b)(1)). As discussed in section V.J.2, we are supplementing § 314.101(d)(3) to more precisely describe the factors that FDA considers in determining whether an ANDA is incomplete on its face.

FDA is revising the definition of “first applicant” to more clearly incorporate the defined term “substantially complete application.” As revised, a first applicant is an ANDA applicant that, on the first day on which a substantially complete application containing a paragraph IV certification is submitted for approval of a drug, submits a substantially complete application that contains, and for which the applicant lawfully maintains, a paragraph IV certification for the drug.

#### V.A.6. Definition of “Postmark”

We proposed to define the term “postmark” to address the MMA’s requirement that a 505(b)(2) or ANDA applicant send notice of its paragraph IV certification within 20 days after the date of the postmark on the notice (i.e., the paragraph IV acknowledgment letter) with which FDA informs the applicant that the application has been filed (see proposed § 314.3(b) and section 505(b)(3)(B)(i) and 505(j)(2)(B)(ii)(I) of the FD&C Act). The purpose of the postmark is to establish a verifiable date from which the 20-day notice period runs. In light of the transition by FDA and regulated industry to electronic communications, FDA proposed to define a “postmark” to mean an independently verifiable evidentiary record of the date on which a document is transmitted, in an unmodifiable format, to another party. For postmarks made by the USPS or a designated delivery service, the date of transmission is the date on which the document is received by the domestic mail service of the USPS or by a designated delivery service. For postmarks documenting an electronic event, the date of transmission is the date (in a

particular time zone) that FDA sends the electronic transmission on its host system as evidenced by a verifiable record. If the sender and the intended recipient are located in different time zones, it is the sender's time zone that provides the controlling date of electronic transmission. In the following paragraphs, we discuss two comments on this proposed definition. After considering these comments, we are finalizing the definition without change.

(Comment 7) One comment recommends that FDA provide ANDA applicants with the option to receive a paragraph IV acknowledgment letter by electronic transmission rather than first class mail to help ensure prompt receipt by the ANDA applicant irrespective of location. The comment suggests that this option may reduce the likelihood that an ANDA applicant would fail to send notice of paragraph IV certification within 20 days after the date of the postmark on the paragraph IV acknowledgment letter, and thereby avoid the administrative consequence described in proposed § 314.101(b)(4). Another comment notes that the proposed definition of postmark clarifies the date by which notice of paragraph IV certification must be sent when ANDA applicants receive a paragraph IV acknowledgment letter from FDA both by electronic mail and the USPS.

(Response 7) We agree that electronic transmission of a paragraph IV acknowledgment letter to an ANDA applicant may facilitate timely sending notice of paragraph IV certification. Our definition of "postmark" is intended to accommodate the electronic transmission of paragraph IV acknowledgment letters from FDA to 505(b)(2) and ANDA applicants in the future.

OGD currently sends an ANDA applicant or its authorized representative a paragraph IV acknowledgment letter (or an acknowledgment letter, if appropriate) in an envelope bearing a postmark made by the USPS. If the ANDA applicant or its authorized representative has

provided an electronic mail address on Form FDA 356h, which accompanies each submission to the ANDA, OGD also sends a courtesy copy of the paragraph IV acknowledgment letter (or an acknowledgment letter, if appropriate) by electronic mail and subsequently archives the electronic communication. Upon the effective date of this final rule (see section VI), the date of FDA's electronic transmission of a paragraph IV acknowledgment letter to an ANDA applicant also will be the postmark described in section 505(j)(2)(B)(ii)(I) of the FD&C Act. We no longer intend to send a paragraph IV acknowledgment letter to an ANDA applicant by the USPS. Accordingly, we expect few circumstances in which there will be a question about which postmark controls for purposes of determining the date by which notice of paragraph IV certification must be sent. However, if an ANDA applicant (or, in the future, a 505(b)(2) applicant) receives a paragraph IV acknowledgment letter from FDA both by electronic mail and the USPS, the earlier postmark provides the controlling postmark.

Although the comment did not discuss 505(b)(2) applications, we note that FDA is committed to adapting its business practices to evolving technology and anticipates electronically transmitting paragraph IV acknowledgment letters to 505(b)(2) applicants in a manner that meets the requirements of the definition of postmark in the future.

#### V.A.7. Definition of "Tentative Approval"

We proposed to define "tentative approval" to mean the notification that an NDA (including a 505(b)(2) application) or ANDA otherwise meets the requirements for approval under the FD&C Act, but cannot be approved because a listed drug has unexpired orphan drug exclusivity, or that a 505(b)(2) application or ANDA otherwise meets the requirements for approval under the FD&C Act, but cannot be approved until the conditions in § 314.107(b)(1)(iii), (b)(3), or (c) are met, because the listed drug has a period of exclusivity

under § 314.108 or section 505A of the FD&C Act, or because a court order under 35 U.S.C. 271(e)(4)(A) orders that the application may be approved no earlier than the date specified (see proposed § 314.3(b) and section 505(j)(5)(B)(iv)(II)(dd)(AA) of the FD&C Act). The proposed definition clarified that a drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval letter after any necessary additional review of the NDA or ANDA. In the following paragraphs, we discuss a comment on this proposed definition. After considering this comment, we are revising the definition to describe an additional basis for tentative approval and making conforming revisions to §§ 314.101(e)(2), 314.105(a) and (d), and 314.107(b)(4) and (d).

(Comment 8) A comment requests that FDA update proposed § 314.107(d) to reflect that Generating Antibiotic Incentives Now (GAIN) exclusivity may delay approval of a 505(b)(2) application or ANDA, and that FDA make any other necessary conforming revisions to the regulations.

(Response 8) We agree with the comment. Title VIII of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144), entitled GAIN, provides an exclusivity period extension for certain designated qualified infectious disease products in section 505E of the FD&C Act. We are revising the definition of “tentative approval” to indicate that approval of a 505(b)(2) application or ANDA also may be delayed by a period of exclusivity for the listed drug under section 505E of the FD&C Act. We are making similar revisions to our regulations on approval of an NDA or ANDA (§ 314.105(a) and (d)) and delay due to exclusivity (§ 314.107(d)). We are also revising our regulations on tentative approval to explain that FDA will issue a tentative approval letter when tentative approval is appropriate in accordance with § 314.107 (see § 314.107(b)(4)).

GAIN also extends by 5 years the 4-year period described in section 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the FD&C Act after which certain 505(b)(2) applications or ANDAs containing a paragraph IV certification may be submitted. Accordingly, we are revising § 314.101(e)(2) to remove the cross-reference to § 314.108(b)(2) and expressly state that FDA will refuse to file an NDA or will consider an ANDA not to have been received if submission of a 505(b)(2) application or an ANDA is not permitted under section 505(c)(3)(E)(ii), 505(j)(5)(F)(ii), or 505E(a) of the FD&C Act. For completeness, we are making a technical amendment to § 314.101(e)(2) to reference pediatric exclusivity under section 505A(b)(1)(A)(i)(I) and (c)(1)(A)(i)(I) of the FD&C Act, which extends by 6 months the 4-year period described in section 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the FD&C Act.

#### V.B. Submission of Patent Information (§ 314.53)

##### V.B.1. General Requirements for Submission of Patent Information (§ 314.53(b) and (c))

Section 314.53(b) of our regulations requires that an applicant submitting an NDA, an amendment to an NDA, or, except as provided in § 314.53(d)(2), a supplement to an approved application, submit the patent information described in § 314.53(c) to its NDA on Forms FDA 3542a and 3542 with the filing or upon and after approval, respectively. The information requested in Form FDA 3542 must be provided for any patent that claims the approved drug substance, approved drug product, or any approved method of using the drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. FDA publishes certain information from Form FDA 3542 in the Orange Book after approval of the NDA or the supplement. The following sections describe our proposed revisions to these regulations and our responses to the comments that we received on the proposed rule.

V.B.1.a. Drug substance (active ingredient) and drug product (formulation or composition) patents. We proposed to revise § 314.53(c)(1) to omit the reference to “complete” patent information and clarify that FDA will accept a submission of patent information on Forms FDA 3542a or 3542, as appropriate, that omits requested patent information if the omission is permitted under an exception in § 314.53(c)(2). We proposed that an applicant need only satisfy the requirements for patent listing set forth in section 505(b)(1) and (c)(2) of the FD&C Act and, subject to the requirements for submission of method-of-use patent information, need not identify each basis on which the patent claims the drug (see proposed § 314.53(c)(2)(i)(S) and (c)(2)(ii)(T)). Accordingly, if a patent is eligible for listing as claiming both the drug substance and the drug product, an applicant only would be required to identify one of these two bases for listing. We proposed to clarify that these proposed exceptions to the required submission of patent information do not alter the requirements for submission of method-of-use patent information (see proposed § 314.53(c)(2)(i)(O)(3) and (c)(2)(ii)(P)(4)).

One comment supports these streamlined requirements for listing patents that claim the drug substance and/or drug product in the Orange Book. In the following paragraphs, we discuss two other comments on these proposed revisions. After considering these comments, we are finalizing these requirements without change. We are making conforming revisions to § 314.53(c)(2)(ii) to replace the phrase “the patent declaration is incomplete” with “the patent declaration does not contain the required information.”

(Comment 9) One comment requests that FDA revise § 314.53(c)(1) to state that FDA will not accept patent information “unless and until” it is submitted on the appropriate form and contains the required information. The comment maintains that this revision would clarify that



submission of patent information is considered complete only as of the date on which all required information has been submitted to FDA.

(Response 9) We decline to revise § 314.53(c)(1) as requested. FDA's existing regulations already require that if an NDA holder timely submits the required patent information, but FDA notifies the NDA holder that its Form FDA 3542 is incomplete or shows that the patent is not eligible for listing, the NDA holder must submit an acceptable Form FDA 3542 within 15 days of FDA's notification to be considered timely filed as of the date of the original submission of patent information (see § 314.53(c)(2)(ii)). FDA believes the current procedure is adequate to ensure timely and complete submission of patent information.

(Comment 10) One comment requests that FDA require additional detail regarding drug substance claims, where the drug product's active ingredient may not be self-evident. The comment also suggests that FDA require more detail regarding drug product claims to enable FDA to determine whether a new patent certification is required for a 505(b)(2) or ANDA applicant's change in product formulation and avoid an unwarranted opportunity for a 30-month stay.

(Response 10) The comment does not clearly describe the additional information requested or provide adequate support for any proposed change. FDA previously has explained that "identification of the relevant patent(s), as opposed to the individual patent claims (other than for method-of-use patents), satisfies the [FD&C Act's] explicit requirements [and] provides sufficient information to potential applicants to determine if a more thorough patent search or analysis is warranted" ("Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of [ANDAs] Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed; Final

Rule” 68 FR 36676 at 36685, June 18, 2003). (The MMA superseded certain provisions of the 2003 Final Rule related to 30-month stays of approval; the superseded regulations were subsequently revoked by technical amendment (see “Application of 30-Month Stays on Approval of [ANDAs] and Certain [NDAs] Containing a Certification That a Patent Claiming the Drug Is Invalid or Will Not Be Infringed; Technical Amendment” (69 FR 11309, March 10, 2004))).) Moreover, it is unnecessary for an NDA holder to submit more detailed patent information regarding drug product claims for purposes of determining whether a 505(b)(2) or ANDA applicant must amend a previously submitted patent certification due to a change in the formulation of its proposed product because the 505(b)(2) or ANDA applicant has an independent duty to evaluate whether a previously submitted patent certification continues to be accurate after any change in the formulation of its proposed drug product. We also are adding §§ 314.60(f)(3) and 314.96(d)(3) to expressly describe when a change in product formulation requires an appropriate patent certification or a recertification (see section V.F.1).

V.B.1.b. Drug substance patents that claim only a polymorph of the active ingredient.

We proposed to revise § 314.53(c)(2)(i)(M)(2) and (c)(2)(ii)(N)(2) to only require an applicant to provide information on whether the patent claims a polymorph (generally, a different crystalline or amorphous form of the same drug substance) that is the same active ingredient described in the NDA, amendment, or supplement if the only basis on which the patent is eligible for listing is that it claims the polymorph. We proposed conforming revisions to § 314.53(b)(1) and (2), (c)(2)(i)(M)(3), and (c)(2)(ii)(N)(3) to provide that the applicant’s certification regarding test data required by § 314.53(b) applies only to patents that claim only a polymorph.

We received two comments that agreed with the proposed provision. In the following paragraphs, we discuss another comment on this proposed revision. After considering the comment, we are finalizing these revisions without change.

(Comment 11) One comment suggests that FDA require more specific information about the polymorph claimed in the patent that is the same active ingredient in the approved drug product to guide development of proposed products intended for submission in a 505(b)(2) application or ANDA.

(Response 11) The comment does not clearly describe the additional information requested; however, we disagree with the premise of the comment. FDA requires the NDA holder to submit information on Form FDA 3542 to enable the Agency to determine whether the patent or patent information is eligible for listing in the Orange Book based on the criteria in our regulations, to enable the Agency to implement section 505(b)(2)(B) and (j)(2)(A)(viii) of the FD&C Act, and to assist the Agency with its administrative listing responsibilities. The drug substance and drug product designation for listing of a patent in the Orange Book is not intended to define the scope of patent claims that an NDA holder or patent owner may assert in patent infringement litigation against a 505(b)(2) or ANDA applicant (see § 314.53(c)(2)(ii)(T)). Each 505(b)(2) or ANDA applicant is responsible for conducting its own analysis of the scope of relevant patents.

V.B.1.c. Method-of-use patents. We proposed to revise § 314.53(b)(1) to further clarify that an NDA applicant or holder may submit a single Form FDA 3542a or Form FDA 3542, as appropriate, for a patent claiming more than one method of use, provided that each method of use is listed separately along with the patent claim number(s) of the patent claim(s) that corresponds to the pending or approved method of use.

We also proposed to revise our regulations to enhance compliance by NDA applicants and holders with the requirements for identifying the specific section(s) of product labeling that corresponds to the method of use claimed by the patent and, upon approval, describing the approved method of use claimed by the patent (the “use code”) required for publication in the Orange Book (see proposed § 314.53(b)(1), (c)(2)(i)(O)(2), (c)(2)(ii)(P)(2) and (3)). To address situations in which the scope of the method of use claimed by the patent is narrower than an indication or other condition of use described in product labeling, we proposed to expressly require that if the scope of the method-of-use claim(s) of a patent does not cover every use of the drug, the applicant must identify only the specific sections of product labeling that correspond to the specific portion(s) of the indication or other condition of use claimed by the patent (see proposed § 314.53(b)(1)). We also proposed that if the scope of the method-of-use claim(s) of the patent does not cover every approved use of the drug, the NDA holder’s use code must describe only the specific portion(s) of the indication or other method of use claimed by the patent (see proposed § 314.53(c)(2)(ii)(P)(3)). Finally, we proposed to codify the Agency’s longstanding requirement that the NDA holder’s use code must contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method-of-use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval (see proposed § 314.53(c)(2)(ii)(P)(3)).

Several comments support FDA’s proposed revisions to the regulations regarding the submission of information on method-of-use patents. In the following paragraphs, we discuss other comments on the submission of information on method-of-use patents. After considering all of these comments, we are making clarifying revisions to § 314.53(b)(1), (c)(2)(i)(O)(1) and

(2), (c)(2)(ii)(P)(1) through (3), and (e), and conforming revisions to Forms FDA 3542a and 3542.

(Comment 12) One comment suggests that the Agency’s proposal regarding the required content of the use code appears to shift to the NDA holder the Agency’s burden of determining whether a 505(b)(2) or ANDA applicant is not seeking approval for a protected use. Another comment objects to FDA’s requirement that the NDA holder’s use code contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method-of-use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval. The comment contends that this approach would require NDA holders to speculate about the protected uses that a prospective 505(b)(2) or ANDA applicant may seek to omit from labeling. Moreover, the comment asserts that this proposal is unworkable given that a 240-character use code may not adequately describe a series of patent claims of varying scope. The comment further notes that the use code does not obviate the need for the 505(b)(2) or ANDA applicant to evaluate the scope of the patent.

(Response 12) FDA disagrees with these comments regarding the content requirements for the use code. Given the Agency’s ministerial role in patent listing, we require an NDA holder to provide adequate information about the scope of a listed method-of-use patent to assist 505(b)(2) and ANDA applicants in assessing whether the listed patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval and to enable FDA to evaluate whether a proposed labeling carve-out is appropriate (see section 505(b)(2)(B) and (j)(2)(A)(viii) of the FD&C Act, respectively; see also Caraco Pharm. Labs. v. Novo Nordisk A/S, 132 S. Ct. 1670, 1684 (2012) (“Use codes are pivotal to the FDA’s implementation of the Hatch-Waxman Amendments”)).

We are finalizing the requirement in § 314.53(c)(2)(ii)(P)(3) that the NDA holder's description of the patented method of use required for publication must contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method-of-use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval, with punctuation changes and clarifying revisions to the parenthetical example. We also are expressly requiring that the NDA holder's description of the patented method of use meets the statutory standard for an NDA holder's submission of patent information (see section 505(b)(1) and (c)(2) of the FD&C Act). As revised, the parenthetical text explains that if the method(s) of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, then the NDA holder must describe only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product (see § 314.53(c)(2)(ii)(P)(3)). We are making conforming revisions to § 314.53(b)(1). The use code must only describe a patented method of use that is described in FDA-approved product labeling because the scope of the approved conditions of use of a drug product is described in the FDA-approved product labeling. We generally describe this content requirement for the use code as the "specific approved method of use claimed by the patent." The development of the use code does not require speculation about the protected uses that a prospective 505(b)(2) or ANDA applicant may seek to omit from labeling; rather, it simply requires the NDA holder to describe only the specific approved method(s) of use claimed by the patent. This requirement also does not shift to the NDA holder the Agency's burden of determining whether a 505(b)(2) or ANDA applicant is not seeking approval for a protected use. Based on the use code provided by the NDA holder, FDA determines the specific labeling that

describes the protected use and decides whether a 505(b)(2) application can be approved with that information omitted from the labeling or, in the case of an ANDA, whether an ANDA that omits the protected information from the labeling will be rendered less safe or effective for its remaining non-protected conditions of use (see § 314.127(a)(7)).

Given that the majority of use codes listed in the Orange Book do not approach 240 characters, this limitation is not expected to affect the accuracy of the NDA holder's description of the specific approved method(s) of use claimed by the patent. Nevertheless, FDA is expanding the use code character limit to 250 characters because FDA's database system can accommodate this additional text. We agree that the use code is not intended to substitute for the 505(b)(2) or ANDA applicant's review of the patent and the approved labeling in making decisions about whether to challenge a listed patent, request a delay in approval until expiry of the listed patent, or not request approval for a use claimed by the listed patent.

(Comment 13) One comment recommends that FDA clarify the directions on Form FDA 3542 for submitting the use code to avoid potential confusion about whether the NDA holder's use code should be based on language from the approved labeling or from the patent claim(s).

(Response 13) FDA agrees with the recommendation to clarify the instructions on Form FDA 3542 and the related regulations regarding the use code. We are revising § 314.53(b)(1) to clarify the general requirement that the NDA holder's description of the patented method of use required by § 314.53(c)(2)(ii)(P)(3) must describe only the approved method(s) of use claimed by the patent (see Response 12 for a discussion of the "specific approved method of use claimed by the patent"). We also are revising § 314.53(c)(2)(i)(O)(1) and (c)(2)(ii)(P)(1) to remove the phrases "or related indication" and "or indication," respectively, and supplementing § 314.53(c)(2)(ii)(P)(3) to clarify that the use code must describe only the specific approved

method of use claimed by the patent. In other words, the scope of the use code must not extend beyond the scope of the patent claim(s) and, within the boundary established by the patent claim(s), the use code must only describe a patented method of use that has been approved by FDA as reflected in approved product labeling (see Caraco Pharm. Labs., 132 S. Ct. 1670 at 1683, n.7 (rejecting an argument that the use code may sweep more broadly than the patent based on the requirement to provide a description of each approved method of use or indication) (emphasis added)). Consistent with our clarifying revisions to § 314.53(c)(2)(ii)(P)(3), we are revising section 4.2b of Form FDA 3542 to state that the NDA holder must submit the description of the specific approved method of use claimed by the patent that is proposed for inclusion as the “use code” in the Orange Book. We also are making conforming revisions to § 314.53(e) to replace the phrase “approved indications or other conditions of use covered by a patent” with the “description of the method of use claimed by the patent as required by § 314.53(c)(2)(ii)(P)(3).”

(Comment 14) One comment proposes that FDA standardize use codes rather than relying on the NDA holder’s description of the approved method of use claimed by the patent. Another comment recommends that FDA further describe its expectations for the content of use codes by providing hypothetical examples in which the patented method-of-use claim is broader, narrower, or co-extensive with an approved indication or other condition of use or that uses different terminology. The comment also suggests that FDA provide advice on the content of the use code where the method of use claimed by the patent is described in a section of labeling other than Indications and Usage.

(Response 14) We decline to adopt standardized use codes because we do not believe that standardized use codes would accurately capture the nuances of the method-of-use patent



claims that NDA holders may submit to FDA for listing. FDA's role in listing patents remains ministerial (see "Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions; Final Rule," 59 FR 50338 at 50349, October 3, 1994; see also 68 FR 36676 at 36687), and we continue to believe that there is a need for accurate and detailed information related to the approved methods of use claimed in the patent being submitted for listing (see 68 FR 36676 at 36682). Since 2003, when we began requiring NDA holders to submit the use code for publication in the Orange Book (see 68 FR 36676 at 36683), the Agency has gained significant experience in implementing section 505(b)(2)(B) and (j)(2)(A)(viii) of the FD&C Act based on the NDA holder's use code. Based on our experience, we are clarifying the use code requirements through this rulemaking. We expect that these clarifying revisions to our regulations will improve the accuracy of use codes. As the U.S. Supreme Court noted in Caraco Pharm. Labs.: "An overbroad use code... throws a wrench into the FDA's ability to approve generic drugs as the statute contemplates" (132 S. Ct. 1670 at 1684). Although we decline to provide hypothetical examples, the following general principles illustrate the clarifying revisions to the regulations regarding the content of use codes.

- Patented method of use is broader than an indication or other approved condition of use:

The use code must only describe a patented method of use that is described in FDA-approved product labeling. If the method of use claimed by the patent uses different terminology than the approved labeling and/or is broader than an indication or other approved condition of use, then the use code would need to be phrased more narrowly than the patent claim to only describe the specific patented method of use that is described in FDA-approved product labeling.

- Patented method of use is co-extensive with an indication or other approved condition of use: The use code must describe only the specific approved method of use claimed by the patent.
- Patented method of use is narrower than an indication or other approved condition of use: If the method of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, then the NDA holder must describe only the specific approved method of use claimed by the patent--not the broader indication or other approved condition of use that may include, but is broader than, the use claimed by the patent.

For example, Prandin (repaglinide) tablets currently are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, and U.S. Patent No. 6,677,358 ('358 patent) was listed in the Orange Book as claiming a method of using Prandin. In Novo Nordisk A/S v. Caraco Pharm. Labs., the Federal Circuit explained that claim 4 of the '358 patent "claims '[a] method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin.' ... An appropriate use code therefore must be limited to use of 'repaglinide in combination with metformin' to treat NIDDM" (688 F.3d 766 at 768 (Fed. Cir. 2012)) (internal citation omitted). A similar approach would apply if the patented method of use is described in a section of labeling other than Indications and Usage. For example, if the patent claims a novel dosing regimen for a particular indication, the use code must specifically describe the protected dosing regimen for that indication and not only the indication to which the dosing regimen relates. Thus, if the method(s) of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, an NDA holder's submission of a use code that

describes an entire indication or other approved condition of use would violate FDA's regulations.

FDA requires the NDA holder to submit an accurate description, subject to the verification under penalty of perjury required by § 314.53(c)(2)(ii)(R), of the specific approved method of use claimed by the patent to implement section 505(b)(2)(B) and (j)(2)(A)(viii) of the FD&C Act. An inaccurate description of the approved method of use claimed by the patent (e.g., one that incorrectly describes the entire indication or condition of use to which the patented method of use relates rather than the specific approved method of use claimed by the patent) would impede FDA's ability to make a scientific determination about whether a 505(b)(2) application or ANDA may be approved with labeling that omits the protected information corresponding to the use code.

As described in § 314.53(b)(1), each approved method of use claimed by the patent must be separately identified and thus will require separate listing(s) of method-of-use information in section 4 of Form FDA 3542. We are revising Forms FDA 3542 and 3542a to facilitate separate listings of method-of-use information. We also are revising § 314.53(c)(2)(ii) to clarify the Agency will not list or publish patent information if it is not provided on Form FDA 3542.

(Comment 15) One comment requests that FDA clarify the level of detail with which an NDA applicant must identify the specific sections of product labeling that correspond to the specific portion(s) of the indication or other condition of use claimed by the patent. Another comment recommends that FDA replace the term "specific sections" with "specific language" and eliminate the parenthetical text in proposed § 314.53(c)(2)(i)(O)(2) and (c)(2)(ii)(P)(2) to clarify that the protected use may encompass less than the entirety of one of the "sections" of the product labeling. This comment also recommends that FDA replace the phrase "corresponds to

the method of use claimed by the patent” with “is claimed by the method of use claimed by the patent” in proposed § 314.53(b)(1), (c)(2)(i)(O)(2), and (c)(2)(ii)(P)(2) to result in a more accurate identification of the specific labeling that describes a protected method of use.

(Response 15) FDA agrees that the regulations should clearly define the requirement to identify the specific labeling that describes the method of use claimed by the patent. FDA is revising its regulations to clarify that, for approved NDAs, the NDA holder submitting information on the method-of-use patent must identify with specificity the section(s) and subsection(s) of the approved labeling that describe the method(s) of use claimed by the patent submitted (see § 314.53(b)(1)). FDA is making conforming revisions to § 314.53(c)(2)(ii)(P)(2) and section 4.2a of Form FDA 3542 with respect to approved labeling, and to § 314.53(c)(2)(i)(O)(2) and section 4.2a of Form FDA 3542a with respect to proposed labeling.

Identifying the section(s) and subsection(s) of the approved labeling with specificity means listing on Form FDA 3542 (or, with respect to proposed labeling, Form FDA 3542a) each section and subsection of labeling that contains information describing the patented method of use.

- For prescription drug products with labeling in the “physician labeling rule” (PLR) format (see “Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products,” 71 FR 3922, January 24, 2006), the section(s) and subsection(s) of the approved labeling should be identified by the section and subsection number (see 21 CFR 201.56(d) and 201.57). For example, “section 1, subsection 1” refers to the first indication listed in approved product labeling (see § 201.57(c)(2)).

- For prescription drug products with labeling not in PLR format, the section(s) and subsection(s) of the approved labeling should be identified by the section and subsection title (see §§ 201.56(b) and (e) and 201.80).
- For nonprescription drug products, the section(s) and subsection(s) of the approved labeling should be identified by the section and subsection title (see 21 CFR 201.66).

An NDA holder should evaluate whether FDA-approved revisions to product labeling (e.g., conversion to PLR format) warrant submission of a revised Form FDA 3542 for the purpose of updating section 4.2a.

FDA agrees that the protected use may comprise less than the entirety of a section or subsection of the approved product labeling. However, it is unnecessary to require an NDA holder to identify the specific language in approved product labeling that describes the patented method of use because the use code and identification of the specific section(s) and subsection(s) of labeling that describe the patented method of use are sufficient for FDA to evaluate a 505(b)(2) or ANDA applicant's proposed labeling. Accordingly, FDA declines to replace the term "specific sections" with "specific language" in § 314.53(c)(2)(i)(O)(2) and (c)(2)(ii)(P)(2). FDA is removing the parenthetical text in proposed § 314.53(c)(2)(i)(O)(2) and (c)(2)(ii)(P)(2) because it is unnecessary in light of other clarifying revisions to the regulations regarding the use code.

If a 505(b)(2) or ANDA applicant submits a statement under section 505(b)(2)(B) and (j)(2)(A)(viii) of the FD&C Act, FDA evaluates the 505(b)(2) or ANDA applicant's proposed labeling to determine whether the applicant is not seeking approval for the protected use based on the use code submitted by the NDA holder and with reference to the labeling section(s) and subsection(s) identified by the NDA holder. FDA determines the specific labeling that describes

the patented method of use, and decides whether the 505(b)(2) application can be approved with that information omitted from the labeling or, in the case of an ANDA, whether an ANDA that carves out the protected information from the labeling would be rendered less safe or effective than the listed drug for the remaining non-protected conditions of use and preclude approval (see § 314.127(a)(7)). For example, FDA has determined that it can approve ANDAs for broad, general indications that may partially overlap with a protected method of use, as long as any express references to the protected use are omitted from the labeling (see Hospira, Inc. v. Burwell, 2014 WL 4406901 at \*17 (D. Md., Sept. 5, 2014) (upholding FDA’s interpretation of section 505(j)(2)(A)(viii) of the FD&C Act)). Although identification of the section(s) and subsection(s) of labeling identified by the NDA holder may assist FDA in exercising its scientific judgment to implement section 505(b)(2)(B) and (j)(2)(A)(viii) of the FD&C Act, FDA is not bound by the section(s) and subsection(s) identified by the NDA holder in section 4.2a of Form FDA 3542 in making its determination. FDA will use its independent scientific judgment to determine which section(s) and/or subsection(s) of labeling contain language that must be carved out based on the use code provided.

FDA agrees that the identified section(s) and subsection(s) of labeling should not merely “correspond” to the method of use claimed by the patent because the term “correspond” could be interpreted in an inappropriately broad manner. To enhance accuracy, FDA is revising § 314.53(b)(1), (c)(2)(i)(O)(2), and (c)(2)(ii)(P)(2) to require that the identified section(s) and subsection(s) of labeling “describe” the method of use claimed by the patent.

(Comment 16) One comment recommends that FDA require NDA holders to resubmit patent information on the updated Form FDA 3542 for all currently listed patents to maintain or revise the Orange Book listing. This comment also suggests that FDA request public comment

on revisions to Forms FDA 3542a and 3542 to conform with the changes described in the proposed rule.

(Response 16) We disagree with the recommendation to require NDA holders to resubmit Form FDA 3542 for all currently listed patents to maintain their current Orange Book listings. Given that over 10,000 patent listings appear in the Orange Book, this recommendation would impose a significant burden on NDA holders and the Agency without a commensurate benefit. If a person seeks to confirm the accuracy or relevance of patent information currently listed in the Orange Book in light of the patent listing requirements set forth in § 314.53(b)(1) and (c), the person may submit a patent listing dispute under § 314.53(f)(1) (see section V.B.4.a). NDA applicants and holders will be required to submit patent information on the updated Forms FDA 3542a and 3542 on a prospective basis.

FDA requested public comment on its proposed revisions to the regulations and has made certain changes to the regulations in response to those comments. FDA is revising Forms FDA 3542a and 3542 to conform to the requirements established by this final rule.

V.B.1.d. Patents previously submitted for listing. We proposed to revise § 314.53(c)(2)(i)(J) and (c)(2)(ii)(K) to remove the requirement that an applicant provide information on whether the patent has been submitted previously for the NDA or supplement. We received no comments regarding this proposed revision; however, we have decided not to finalize this proposed change. Instead, we have decided to retain the existing requirement to assist the Orange Book staff with updating listed patent information where appropriate (see 68 FR 36676 at 36686 and “Agency Information Collection Activities; Submission for [OMB] Review; Comment Request; Applications for [FDA] Approval to Market a New Drug...,” 72 FR 21266 at 21269, April 30, 2007).

V.B.1.e. Reissued patents. We proposed to require an NDA holder to submit additional information on patents that have been reissued by the USPTO under 35 U.S.C. 251. We proposed that an NDA applicant or holder must include information on whether a patent submitted for listing is a reissuance of a patent previously submitted for listing for the NDA or supplement (see proposed § 314.53(c)(2)(i)(J) and (c)(2)(ii)(K)). Our proposal reflected our consideration of the original patent and the reissued patent as a “single bundle of patent rights,” albeit patent rights that may have changed with reissuance, for purposes of administering the patent certification requirements of the FD&C Act and any 30-month stay of approval or 180-day exclusivity that relates to a paragraph IV certification to the original patent. In the following paragraphs, we discuss three comments on this proposal (see section V.E.3 for a discussion of comments on patent certification requirements for reissued patents). After considering these comments, we are not finalizing this proposal.

(Comment 17) The first comment recommends that FDA reevaluate its proposed regulations on reissued patents in light of a recent court decision rejecting FDA’s “single bundle of patent rights” approach in a case involving the pre-MMA version of the FD&C Act. The second comment suggests that FDA further consider its “single bundle of patent rights” approach given the possibility for issuance of multiple patents based on continuing applications referring to the original patent application. The third comment supports the business certainty provided by FDA’s “single bundle of patent rights” approach because the requirement for a 505(b)(2) or ANDA applicant to provide an appropriate patent certification or statement for a reissued patent would be governed by the provisions regarding untimely filed patents if either the original patent or the reissued patent was late-listed as to a pending 505(b)(2) application or ANDA.



(Response 17) FDA agrees that the “single bundle of patent rights” approach reflected in its proposed regulations on reissued patents should not be finalized in light of the recent decision in Mylan Pharms., Inc. v. FDA, 594 Fed. Appx. 791 (4<sup>th</sup> Cir. Dec. 16, 2014). In Mylan, the Court determined that a reissued patent “is a separate grant of rights, even if elements of the reissued patent overlap with those of the original patent” (see 594 Fed. Appx. 791 at 797). The Court held that the statutory reference to “the patent which is the subject of the certification” in the pre-MMA version of section 505(j)(5)(B)(iv) of the FD&C Act means that each patent (original and/or reissued) that is the subject of a paragraph IV certification may be a basis for eligibility for 180-day exclusivity.

Although the Mylan decision involved the pre-MMA version of the FD&C Act (in which eligibility for 180-day exclusivity was evaluated on a patent-by-patent basis), the Court’s interpretation of “the patent which is the subject of the certification” is relevant to the current version of the FD&C Act when determining eligibility for first applicant status under the MMA’s 180-day exclusivity scheme (see section 505(j)(5)(B)(iii) of the FD&C Act). Accordingly, the Agency now considers reissued patents as separate and distinct from the original patent for purposes of administering the patent certification requirements of the FD&C Act and any 30-month stay of approval or 180-day exclusivity. Given that a reissued patent will be treated no differently than an original patent, it is unnecessary for FDA to require that an NDA holder’s submission of patent information include information on whether the patent is a reissued patent of a patent previously submitted for listing, and we are not finalizing proposed § 314.53(c)(2)(i)(J) and (c)(2)(ii)(K).

Upon patent reissuance, the original patent is surrendered and ceases to have legal effect (see 37 CFR 1.178(a)). Thus, an NDA holder is required to withdraw the original patent and

request that the original patent be removed from listing in the Orange Book after patent reissuance (see § 314.53(f)(2)). Consistent with our policy for any request to remove a patent from listing in the Orange Book, an original patent that has been reissued would remain listed in the Orange Book until FDA determined that no first applicant is eligible for 180-day exclusivity based on a paragraph IV certification to that patent or after the 180-day exclusivity period of a first applicant based on that patent has expired or has been extinguished.

V.B.2. When and Where To Submit Patent Information (§ 314.53(d))

V.B.2.a. Submission of patent information for NDA supplements (§ 314.53(d)(2)). We proposed to revise § 314.53(d)(2) to create two broad categories of supplements for purposes of required submission of patent information. For supplements that seek approval for a change that would result in a new entry in the Orange Book (e.g., a change to the dosage form, route of administration, strength, or prescription drug status), we proposed that an applicant would continue to submit the complete patent information required under § 314.53(c) with submission of the supplement and following approval, respectively. For supplements that seek approval for another type of change (e.g., to change the formulation, to add a new indication or other condition of use, or to make any other patented change regarding the drug substance, drug product, or any method of use that would not result in a new entry in the Orange Book), we proposed that the patent information submission requirements would depend on whether the existing patent information submitted to FDA for the product approved in the original NDA continued to claim the changed product.

If the patents listed for the approved NDA also claim the drug or method of using the drug for which approval is sought in the NDA supplement, we proposed that we would permit an applicant to submit a statement declaring that the patent(s) currently listed for a specific NDA

(identified by NDA number and product number as listed in the Orange Book) continue to claim the drug or method of using the drug for which approval is sought in the NDA supplement, if this statement is accompanied by the signed patent declaration verification required by § 314.53(c)(2)(i)(Q) and (c)(2)(ii)(R) and if patent information required by § 314.53(c)(2)(ii) previously was submitted. If, however, a listed patent no longer claims the product as changed by the supplement, then we proposed that the applicant must submit a request to correct or remove the patent information from the list at the time of approval of the supplement (see proposed § 314.53(f)(2)). Correspondingly, if one or more existing patents claim the product as changed by the supplement and this patent information has not been submitted to FDA, we proposed that the applicant must submit the patent information with the supplement and following approval of the supplement. We proposed a conforming revision to § 314.70(f) to clarify that an applicant that submits a supplement to an NDA also must comply with the patent information requirements under § 314.53.

One comment supports the proposal because it would reduce duplicative submissions of patent information for supplements. We are finalizing proposed § 314.53(d)(2)(i) with an editorial change to clarify that § 314.53(d)(2)(i)(A) and (B) also apply to a supplement that seeks to add (rather than change) a dosage form, route of administration, or strength. To facilitate implementation of this provision, we are revising § 314.53(c)(2)(i)(F) and (c)(2)(ii)(F) to require that the NDA applicant or holder, respectively, identify the dosage form(s), route(s) of administration and whether the drug is proposed or approved for prescription use or over-the-counter (OTC) use in its submission of patent information. We are making conforming revisions to Forms FDA 3542a and 3542.

We are making several clarifying revisions to proposed § 314.53(d)(2)(ii). The proposed rule explained that we would permit an NDA holder to submit a statement declaring that the patent(s) currently listed for a specific NDA continue to claim the drug or method of using the drug for which approval is sought in the NDA supplement (instead of resubmitting the patent information with the NDA supplement), if this statement is accompanied by a signed patent declaration verification (see 80 FR 6802 at 6823). Consistent with the intent of the proposed rule to reduce duplicative submissions of patent information and enhance efficiency, we are not requiring an NDA holder to submit a statement with an NDA supplement if the NDA holder is not required to resubmit patent information pursuant to § 314.53(d)(2)(ii)(A). Accordingly, if an NDA supplement is approved for a change other than one of the changes listed in § 314.53(d)(2)(i) and the NDA holder does not submit Form FDA 3542 or submit a request to withdraw the patent or patent information from the list under § 314.53(f)(2)(iv) (see § 314.53(d)(2)(ii)(B) and (C)), FDA will consider the NDA holder to have affirmed that any currently listed patent(s) continues to claim the drug product as changed by the supplement. We are revising § 314.53(d)(2)(ii)(A) to clarify that patent information already submitted to FDA refers to information required by § 314.53(c). We also are revising § 314.53(d)(2)(ii)(A) to clarify that the requirement to resubmit patent information with a supplement if the description of the patented method of use would change upon approval of the supplement refers to the published description of the patented method of use (i.e., the use code).

We are making a conforming revision to § 314.53(c) to clarify that if the applicant submits a supplement for a change other than one of the changes listed under § 314.53(d)(2)(i), then the patent information submission requirements of § 314.53(d)(2)(ii) apply (see § 314.53(c)(2)(i)(S)(3) and (c)(2)(ii)(T)(3)).

V.B.2.b. Untimely filing of patent information (§§ 314.53(d)(3), 314.50(i)(4), and 314.94(a)(12)(vi)). We proposed to revise our regulations regarding the submission of information on patents issued after the approval of an NDA or supplement to expressly describe our longstanding practice with respect to listing patent information that is not timely filed (see proposed § 314.53(d)(3)). Proposed § 314.53(d)(3) stated that if a patent is issued after approval and the required patent information is not submitted within 30 days of the issuance of the patent, FDA will list the patent, but patent certifications will be governed by the provisions regarding untimely filed patents in §§ 314.50(i)(4) and (6) and 314.94(a)(12)(vi) and (viii). We also proposed to revise §§ 314.50(i)(4) and 314.94(a)(12)(vi) to state that, except as provided in § 314.53(f)(1), an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent ("use code") will be considered untimely filing of patent information if:

- The amendment is submitted more than 30 days after patent issuance and it is not related to a corresponding change in approved product labeling; or
- The amendment is submitted more than 30 days after a corresponding change in approved product labeling.

Two comments agreed with this proposal. In the following paragraphs, we discuss two other comments on the proposal for certain amendments to the description of the approved method of use claimed by the patent to be considered untimely filing of patent information. After considering these comments, we are making clarifying revisions to the regulations and describing an additional set of circumstances in which an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will not be considered untimely filing of patent information.

(Comment 18) One comment recommends that FDA withdraw its proposal, given that changes in patent law or interpretation, developments in patent-specific litigation, and/or proceedings before the USPTO may affect the scope of a patent claim's coverage and necessitate revisions to the use code. The comment notes that these events typically occur more than 30 days after patent issuance and do not involve a corresponding change in product labeling. Another comment recommends that FDA reevaluate its proposal to consider certain changes to the use code as untimely filed patent information in light of the lack of clarity on setting use codes.

(Response 18) We decline to withdraw our proposal given the important role of use codes in enabling a 505(b)(2) or an ANDA applicant to state that it is not seeking approval for the method of use claimed by the patent (see section 505(b)(2)(B) and (j)(2)(D)(viii) of the FD&C Act). However, we agree that revisions to the use code may be appropriate in other limited circumstances, as reflected in our revisions to §§ 314.50(i)(4) and 314.94(a)(12)(vi). Our approach is intended to enhance the accuracy of use codes and ensure that 505(b)(2) and ANDA applicants have timely notice of changes to the asserted patent coverage for a listed drug, while reducing opportunities for manipulation of patent use codes.

As a preliminary matter, we are revising the regulations to more clearly describe the circumstances in which an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will not be considered untimely filing of patent information (see §§ 314.50(i)(4)(i)(A) and (B) and 314.94(a)(12)(vi)(A)(1) and (2)). As revised, an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will be considered timely filed if it is submitted within 30 days of patent issuance or within 30 days of approval of a corresponding change to product labeling. We also are revising

the regulations to provide that an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will be considered timely filed patent information if it is submitted within 30 days of a decision by the USPTO or a Federal court that is specific to the patent and alters the construction of a method-of-use claim(s) of the patent (see §§ 314.50(i)(4)(i)(C) and 314.94(a)(12)(vi)(A)(3)). The amendment must contain a copy of the USPTO or court decision, and the accompanying Form FDA 3542 must identify the decision as a change related to the patent in section 1.h of the form (see the following discussion regarding revisions to § 314.53(c)(2)(i)(K) and (c)(2)(ii)(L)).

Our addition of §§ 314.50(i)(4)(i)(C) and 314.94(a)(12)(vi)(A)(3) permits NDA holders to make timely revisions to the use code based on a patent-specific decision by the USPTO (e.g., inter partes review, post-grant review, and reexamination) or by a Federal court (e.g., Markman hearing) that construes the terms of the patent claim(s). An NDA holder may submit a revised use code based on a patent-specific decision by either a Federal district court, the Court of Appeals for the Federal Circuit, or the U.S. Supreme Court. We decline to broaden the scope of this provision to allow for use code changes to be considered timely filed based solely on changes in patent law or interpretation that are not specific to the patent for which the use code was submitted because we are not experts in patent law and would be unable to evaluate arguments that could effectively remove the limitation for untimely filing of method-of-use patent information.

Our clarifying revisions to the regulations are expected to address concerns about how to set use codes, and there is no need to reevaluate our proposal on this basis.

To facilitate implementation of this provision, FDA is revising § 314.53(c)(2)(i)(K) and (c)(2)(ii)(L) to require that if the patent has been submitted previously for listing, the NDA

holder must identify all change(s) from the previously submitted patent information and specify whether the change is related to the patent (e.g., patent term extension or patent-specific decision by the USPTO or a Federal court) or related to an FDA action or procedure (e.g., FDA approval of a supplement that changes the approved conditions of use of the drug). This information will assist the Orange Book staff in updating listed patent information where appropriate and replaces the current requirement that an applicant only identify whether the expiration date is a new expiration date.

We also are making technical amendments in §§ 314.50(i)(4) and 314.94(a)(12)(vi) to explain that a 505(b)(2) or ANDA applicant generally is not required to submit a patent certification or statement to address the patent or patent information that is late-listed with respect to the pending 505(b)(2) application or ANDA. Although a patent certification or statement generally would not be required in this circumstance, we would permit an applicant to submit and maintain a patent certification (including a paragraph IV certification) or a statement pursuant to section 505(b)(2)(B) or 505(j)(2)(B)(viii) of the FD&C Act, if desired. For example, an ANDA applicant may wish to submit a paragraph IV certification to challenge the method-of-use patent with the revised use code if the applicant may be eligible for 180-day exclusivity based on that certification.

V.B.2.c. Where to send submissions of Forms FDA 3542a and 3542 (§ 314.53(d)(4)).

We proposed to clarify that patent information submitted on Form FDA 3542a with the filing of an NDA, amendment, or supplement must be submitted to the CDER Central Document Room, and should not be submitted to the Orange Book staff (see proposed § 314.53(d)(4)(i); see also §§ 314.50(h) and 314.70(f)). We also proposed to require that patent information submitted on Form FDA 3542 upon and after approval of an NDA or supplement be submitted directly to the



Orange Book staff through the OGD Document Room. Our proposal to designate the OGD Document Room as the official repository for submission of Form FDA 3542 was intended to facilitate prompt listing of patent information in the Orange Book after Form FDA 3542 has been officially received by the Agency (see proposed § 314.53(d)(4)(ii) and (d)(5)).

In the following paragraphs, we discuss a comment on these proposed revisions. After considering this comment, we are finalizing § 314.53(d)(4)(ii) with revisions to maintain the CDER Central Document Room as the official repository for submission of Form FDA 3542 and we are finalizing § 314.53(d)(4)(i) and (ii) to clarify that Forms FDA 3542a and 3542 can be submitted electronically. We also are finalizing § 314.53(d)(4)(i) and (ii) with an editorial correction to the title of Forms FDA 3542a and 3542, and we are making the same correction in § 314.53(f)(2)(ii) through (iv).

(Comment 19) One comment requests confirmation that NDA holders may submit Form FDA 3542 to the OGD Document Room through the Electronic Submissions Gateway (ESG). The comment also recommends that FDA clarify that Form FDA 3542a must be submitted to the NDA via CDER's Central Document Room.

(Response 19) FDA is revising § 314.53(d) to expressly provide that Form FDA 3542 can be submitted in an electronic format submission that complies with § 314.50(l)(5), which permits submission through the ESG. This revision and the corresponding revision to § 314.53(d)(5) are intended to clarify how submission dates are determined for Form FDA 3542, given the implications of untimely filing of patent information on the patent certification obligations of 505(b)(2) and ANDA applicants that rely upon the listed drug (see §§ 314.50(i)(4) and 314.94(a)(12)(vi)). Beginning in May 2017, Form FDA 3542 and other submissions under section 505(b), (i), and (j) of the FD&C Act must be submitted in the electronic format specified

by FDA (see section 745A(a) of the FD&C Act (21 U.S.C. 379k-1(a)) and guidance for industry entitled “Providing Regulatory Submissions in Electronic Form--Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications” (May 2015), available at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>).

Accordingly, we only have specified the method of submission where it is important to describe how receipt dates or submission dates are determined for a particular type of submission.

Based on the transition to electronic submission of Form FDA 3542 and related changes in FDA’s administrative processes, we are not finalizing our proposal to change the official repository for submission of Form FDA 3542. Thus, Form FDA 3542 must continue to be submitted to the NDA via the CDER Central Document Room or the ESG. The CDER Central Document Room and the ESG promptly direct submissions of Form FDA 3542 to the Orange Book staff for listing in the Orange Book. To ensure that patents and patent information are listed in the Orange Book only after Form FDA 3542 has been officially received by FDA, the Orange Book staff intends to rely only on submissions of Form FDA 3542 that are received from the Central Document Room and disregard any duplicate copies or courtesy copies of Form FDA 3542 that are submitted through other channels. We are revising § 314.53(d)(4)(ii) to emphasize that Form FDA 3542 should not be submitted to the Orange Book staff.

V.B.2.d. Submission date of patent information (§ 314.53(d)(5)). We proposed to revise § 314.53(d)(5) to establish that the submission date of patent information provided by an NDA holder after approval of an application is the earlier of the date on which Form FDA 3542 is date-stamped by the OGD Document Room or officially received electronically by FDA through the ESG (i.e., at the completion of electronic transmission). We proposed that patent information

sent to another location at FDA would not be considered received by FDA for purposes of § 314.53(d)(3) on timely filing and a 505(b)(2) or ANDA applicant's patent certification obligations pursuant to § 314.50(i)(4) and (6) or § 314.94(a)(12)(vi) and (viii), respectively, unless it is sent to the official repository identified in the regulation. In the following paragraphs, we discuss two comments on this provision. After considering these comments, we are finalizing § 314.53(d)(5) with revisions unrelated to the comments to conform to the changes made to § 314.53(d)(4)(ii).

(Comment 20) One comment suggests that FDA provide a list of untimely filed patent information to facilitate evaluation of patent certification obligations by 505(b)(2) and ANDA applicants. Another comment recommends that FDA include in the Orange Book the date on which the patent information was submitted to FDA.

(Response 20) FDA agrees that modifying the Orange Book to list the date on which patent information was submitted to FDA as described in § 314.53(d)(5) would enable applicants to determine whether a patent is late-listed as to a pending 505(b)(2) application or ANDA and avoid the need for applicants to contact the Orange Book staff for this information. FDA intends to list the date of submission of patents and patent information in the Orange Book on a prospective basis beginning as soon as practicable after the effective date of this rule. This addition to the Orange Book does not require any modification to the regulations. FDA does not intend to separately publish a list of untimely filed patent information.

#### V.B.3. Public Disclosure of Patent Information (§ 314.53(e))

We proposed technical corrections to § 314.53(e) to delete the reference to monthly supplements to the Orange Book and clarify that copies of the "submitted patent information" (rather than copies of the "file") may be requested from FDA's Freedom of Information Staff.

We also proposed to expressly state that the submitted patent information, and requests for delisting patents, will be subject to public disclosure (see proposed § 314.53(e)). In the preamble to the proposed rule, we explained that FDA may elect to proactively post on FDA's Web site a copy of the submitted patent information (Form FDA 3542) for listed patents in advance of a request under the Freedom of Information Act (FOIA) based on our anticipation of requests for this information. In the following paragraphs, we discuss a comment on the potential for proactive posting of Form FDA 3542 on FDA's Web site. After considering this comment, we are making an editorial correction to clarify the information that may be subject to public disclosure.

(Comment 21) One comment urges FDA not to proactively post Form FDA 3542 on the FDA Web site based on concerns that the patent information could be misused or lead to misinterpretation of the scope of relevant patent rights in litigation or commercial contexts.

(Response 21) FDA is not persuaded by the comment, given that Form FDA 3542 must contain the verification required by § 314.53(c)(2)(ii)(R) and may be subject to disclosure under FOIA and applicable disclosure regulations. Moreover, FDA has advised prospective 505(b)(2) and ANDA applicants that the use code and other information provided on Form FDA 3542 is not meant to substitute for the applicant's review of the patent. However, at this time, FDA does not intend to proactively post Form FDA 3542 for patent information submitted for listing in the Orange Book because there is an adequate mechanism to obtain a Form FDA 3542 on an individual basis through a FOIA request. We are revising § 314.53(e) to clarify that the submitted patent information and requests to remove a patent or patent information from the list may be subject to public disclosure.

V.B.4. Correction or Change of Patent Information (§ 314.53(f))

V.B.4.a. Requests by persons other than the NDA holder (§ 314.53(f)(1)). We proposed to revise § 314.53(f) to clarify and improve the mechanism for challenging the accuracy or relevance of patent information submitted to the Agency under § 314.53 and listed in the Orange Book (see proposed § 314.53(f)(1)). First, we proposed to establish a 30-day timeframe in which the NDA holder would be required to respond to FDA's request to confirm the correctness or omission of patent information to facilitate timely resolution of the patent listing dispute. Second, we proposed enhanced procedures to govern challenges to the accuracy or relevance of an NDA holder's submission of method-of-use patent information so that the Agency has additional information to implement section 505(b)(2)(B) and (j)(2)(A)(viii) of the FD&C Act in cases where the accuracy or relevance of the use code is disputed (see proposed § 314.53(f)(1)).

For a patent listing dispute regarding method-of-use patent information, we proposed to ask the NDA holder to confirm the correctness of its description of the approved indication or method of use that has been included as the "use code" in the Orange Book, and provide information on the specific approved use claimed by the patent that would enable the Agency to make a determination in accordance with section 505(b)(2)(B) or (j)(2)(A)(viii) of the FD&C Act (see proposed § 314.53(f)(1)). We proposed that if the NDA holder confirms the accuracy of its submitted patent information in response to FDA's request, fails to timely respond to the request, or submits a revision to the use code that does not provide adequate clarity for FDA to determine whether the scope of a proposed labeling carve-out would be appropriate based on the NDA holder's use code and approved labeling, FDA would review a proposed labeling carve-out(s) for the 505(b)(2) application or ANDA with deference to the 505(b)(2) or ANDA applicant's interpretation of the scope of the patent. In such a case, we explained that FDA would consider the use code and labeling information submitted by the NDA holder on Form

FDA 3542, the history of labeling changes related to approval of an indication(s) for the drug product, the 505(b)(2) or ANDA applicant's interpretation of the scope of the patent, the need for consistent labeling among products approved under section 505(j) of the FD&C Act, and the requirements of §§ 314.94(a)(8)(iv) and 314.127(a)(7), as appropriate.

Two comments support FDA's proposed revisions to the patent listing dispute procedure. In the following paragraphs, we discuss several other comments on this proposal. After considering these comments, we are revising § 314.53(f)(1) to describe the rules that will apply to patent listing disputes involving drug substance, drug product, and method-of-use claims. We also are revising § 314.53(c)(2)(ii)(R) to expressly state that the requirement to verify the accuracy and completeness of the submission of patent information applies to a response to a patent listing dispute under § 314.53(f)(1). We intend to take a stepwise approach and evaluate whether FDA's revisions to the regulations on submission of method-of-use patent information (see § 314.53(b)(1) and (c)(2)) and patent listing dispute procedures adequately address the problem of overbroad and ambiguous use codes before we establish a process to review a proposed labeling carve-out with deference to the 505(b)(2) and/or ANDA applicant(s)' interpretation of the scope of the patent. Therefore, at this time, we are not finalizing our proposal to review a proposed labeling carve-out with deference to the applicant(s)' interpretation of the scope of the patent in certain circumstances. We will continue to consider whether there is a need to finalize this proposal in the future.

(Comment 22) Three comments indicate that there are inconsistencies between the text of proposed § 314.53(f) and the process described in the corresponding preamble, and request that FDA clarify the circumstances in which the Agency proposes to review a proposed labeling carve-out for a 505(b)(2) application or ANDA with deference to the 505(b)(2) or ANDA

applicant's interpretation of the scope of the patent. Several comments contend that it is inappropriate to defer to the 505(b)(2) or ANDA applicant's interpretation of the scope of the patent where the NDA holder has confirmed the accuracy of the use code. One comment asserts that this approach will encourage 505(b)(2) and ANDA applicants to routinely dispute method-of-use patent information in an attempt to receive deference on a narrow interpretation of the method-of-use patent and submit a statement under section 505(b)(2)(B) or (j)(2)(A)(viii) of the FD&C Act instead of a patent certification. One comment also contends that the Agency's standard for determining that an NDA holder's revision to the use code "does not provide adequate clarity" or determining that there is "insufficient information" to evaluate a proposed labeling carve-out is impermissibly vague.

(Response 22) FDA has made multiple changes to address the issue of overbroad and ambiguous use codes, including revisions to the regulations on submission of patent information and revisions to the patent listing dispute procedures (see sections V.B.1.c and V.B.2.b). We initially intend to evaluate whether these revisions to the regulations adequately address the problem of overbroad and ambiguous use codes. If these revisions to our regulations do not adequately address the problem, we will further consider whether to finalize the proposal to review a proposed labeling carve-out for a 505(b)(2) application or ANDA with deference to the 505(b)(2) and/or ANDA applicant(s)' interpretation of the scope of the patent. If FDA decides to finalize the proposal, FDA would clarify the process and the circumstances in which such deference may be given.

We are revising the regulation to provide a more detailed description of the procedure for patent listing disputes directed to the accuracy or relevance of submitted patent information regarding an approved method of using the drug product (see § 314.53(f)(1) and (f)(1)(i)(B); see

also § 314.53(f)(1)(i)(A) (describing patent listing dispute procedures directed to drug substance or drug product claims)). We also are revising § 314.53(c)(2)(ii)(R) to expressly state that the requirement that an NDA holder verify the accuracy and completeness of the submission of patent information applies to a response to a request under § 314.53(f)(1). This regulatory approach is intended to provide the Agency with additional information to facilitate implementation of section 505(b)(2)(B) and (j)(2)(A)(viii) of the FD&C Act (see section 701(a) of the FD&C Act).

For all patent listing disputes, we are requiring that the patent listing dispute communication contain a statement of dispute that describes the specific grounds for disagreement regarding the accuracy or relevance of patent information for FDA to send to the applicable NDA holder. If a person disputes the accuracy or relevance of submitted patent information regarding an approved method of using the drug product, this statement of dispute must be only a narrative description (no more than 250 words) of the person's interpretation of the scope of the patent with respect to the method of use.

FDA intends to forward the statement of dispute (without review or redaction) to the applicable NDA holder using the electronic mail (email) address or facsimile (fax) number provided by the NDA holder on the most recent Form FDA 356h submitted to the NDA. Therefore, the person submitting the patent listing dispute communication should clearly identify the statement of dispute that he or she intends for FDA to send to the applicable NDA holder, and only include information for which the person consents to disclosure.

- For patent listing disputes directed to drug substance or drug product claims, the NDA holder must confirm the correctness of the patent information and include the signed verification required by § 314.53(c)(2)(ii)(R) or withdraw or amend the patent



information in accordance with § 314.53(f)(2) within 30 days of the date on which the Agency sends the statement of dispute. Although proposed § 314.53(f)(1) would have permitted disputes over the omission of patent information, it is unnecessary for FDA to request the NDA holder to confirm the omission of patent information for a listed patent because we no longer require an NDA holder to identify whether a patent claims both the drug substance and the drug product (see § 314.53(c)(2)(ii)(T)). Accordingly, we are making a conforming amendment to remove the phrase “or omission of patent information” from § 314.53(f)(1)(i)(A). Unless the NDA holder withdraws or amends its patent information in response to the patent listing dispute, the Agency will not change the patent information in the Orange Book (see § 314.53(f)(1)(i)(A)).

- For patent listing disputes directed to method-of-use claims, the NDA holder must confirm the correctness of the NDA holder’s description of the approved method of use claimed by the patent that has been included as the “use code” in the Orange Book or withdraw or amend the patent information in accordance with § 314.53(f)(2). In either case, the NDA holder must provide a narrative description (no more than 250 words) of the NDA holder’s interpretation of the scope of the patent that explains why the existing or amended “use code” describes only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. The NDA holder must also include the signed verification required by § 314.53(c)(2)(ii)(R) and submit its response within 30 days of the date on which the Agency sends the statement of dispute (see § 314.53(f)(1)(i)(B)). Any response from the NDA holder that is submitted after 30 days will be considered untimely. The narrative

description must only contain information for which the NDA holder consents to disclosure because FDA will send the text of the statement to the person who submitted the patent listing dispute without review or redaction to further assist the person (generally a 505(b)(2) or ANDA applicant, a prospective applicant, or its representative) in determining whether a use for which an applicant may seek approval is a protected use.

We are revising the regulation to clarify that if the NDA holder timely responds to the patent listing dispute with a confirmation of the correctness of the patent information, the narrative description required by § 314.53(f)(1)(i)(B), and the signed verification required by § 314.53(c)(2)(ii)(R), the Agency will not change the patent information in the Orange Book (see § 314.53(f)(1)(i)(B)(1)). We are also revising the regulation to more clearly state that if the NDA holder timely responds to FDA's request with revised patent information, the narrative description required by § 314.53(f)(1)(i)(B), and the signed verification required by § 314.53(c)(2)(ii)(R), FDA will update the Orange Book to reflect the revised patent information (see § 314.53(f)(1)(i)(B)(2) and Response 26). This approach provides additional clarity, and establishes a mechanism for a person (including a 505(b)(2) or ANDA applicant) to request that an NDA holder confirm compliance with the updated requirements for submission of patent information described in § 314.53(b) and (c).

A 505(b)(2) application or ANDA must contain an appropriate certification or statement for each listed patent, including the disputed patent, during and after the patent listing dispute (see § 314.53(f)(1)(ii)). A disputed method-of-use patent may continue to be the subject of a paragraph IV certification. We do not believe that an ongoing patent listing dispute process will have an impact on the timing of approval of a 505(b)(2) application or ANDA that is otherwise eligible for approval and relies on the listed drug for which the disputed patent is listed in the

Orange Book. FDA may consider the narrative description from the NDA holder required by § 314.53(f)(1)(i)(B), as appropriate, to assist FDA in exercising its scientific judgment to implement section 505(b)(2)(B) and (j)(2)(A)(viii) of the FD&C Act.

To advise prospective and pending 505(b)(2) or ANDA applicants of a patent listing dispute involving a method-of-use patent, FDA will promptly post information about the patent listing dispute on a Web page linked to the Orange Book. FDA intends to provide information such as the relevant drug product, NDA number, NDA holder, U.S. Patent Number, relevant use code(s), and whether the NDA holder has timely responded to the patent listing dispute (see § 314.53(f)(1)(iii)).

(Comment 23) Three comments recommend that FDA withdraw or revise the proposal to review, in certain circumstances, a proposed labeling carve-out for a 505(b)(2) application or ANDA with deference to the 505(b)(2) or ANDA applicant's interpretation of the scope of the patent. One comment contends that there is no basis for FDA's proposed approach because the statutory scheme contemplates that disputes over the scope of a method-of-use patent will be resolved by Federal courts in patent infringement litigation, especially given that the MMA established a counterclaim procedure in which a 505(b)(2) or ANDA applicant may seek an order requiring the NDA holder to correct or delete the submitted patent information. Another comment maintains that it would be legally inappropriate for FDA to defer to the 505(b)(2) or ANDA applicant's view of the scope of a patent that the applicant does not own, especially if the NDA holder has confirmed the accuracy of the use code. Two comments suggest that when patent listing disputes arise, FDA should seek clarification or correction of patent information through other means.

(Response 23) We believe that FDA has the authority to establish a regulation describing the limited circumstances in which the Agency would defer to the 505(b)(2) or ANDA applicant's interpretation of the scope of a patent that it does not own. However, in light of the incremental approach that we are taking to this issue, we are not finalizing this aspect of our proposal at this time. We will continue to consider whether there is a need to finalize this proposal in the future.

The statutory provisions that permit a 505(b)(2) or ANDA applicant to submit a statement that a listed patent does not claim a use for which the applicant is seeking approval complement the patent certification requirements (see section 505(b)(2)(A) and (B) and (j)(2)(A)(vii) and (viii) of the FD&C Act). FDA's revised regulations are intended to preserve FDA's ministerial role in listing patents (see 59 FR 50338 at 50349 and 68 FR 36676 at 36683 and 36687) and to also address ambiguous or overbroad use codes that could be a barrier to approval of a 505(b)(2) application or ANDA for uses that are not claimed by the listed patent (see § 314.53(b)(1), (c)(2)(ii)(P)(3), and (f)(1)). If an NDA holder provides a timely response to a patent listing dispute and a 505(b)(2) or ANDA applicant disagrees with the NDA holder's response to the patent listing dispute (or disagrees with the use code), the 505(b)(2) or ANDA applicant may submit a paragraph IV certification to challenge the method-of-use patent and assert a counterclaim in the context of an infringement action or pursue a declaratory judgment action, as appropriate, to obtain patent certainty (see section 505(c)(3)(D)(i) and (ii) and (j)(5)(C)(i) and (ii) of the FD&C Act).

We disagree, however, that the counterclaim procedure in section 505(c)(3)(D)(ii) and (j)(5)(C)(ii) of the FD&C Act obviates the need for an enhanced patent listing dispute procedure. Nothing in the FD&C Act precludes FDA from developing a procedure for patent listing disputes

in light of our broad authority to issue regulations for the efficient enforcement of the FD&C Act. As the U.S. Supreme Court observed in Caraco Pharm. Labs., “the counterclaim cannot restore the smooth working of a statutory scheme thrown off kilter by an overly broad use code. At best, it permits the generic manufacturer to do what the scheme contemplates it should do-- file an ANDA with a section viii statement--but only after expensive and time-consuming litigation. A fix is in order, but it must come from Congress or FDA” (132 S.Ct. 1670 at 1689).

Finally, we note that comments recommending that FDA seek clarification or correction of patent information through other means do not describe an alternative to the approach we proposed. We believe that the modifications that we have made to the patent listing dispute procedure, discussed in Response 22, and our stepwise approach to evaluating whether FDA’s revisions to this procedure and the regulations on submission of method-of-use patent information address the problem of overbroad and ambiguous use codes, adequately address the comments received on our proposal.

(Comment 24) Three comments assert that FDA’s proposed deference to the 505(b)(2) or ANDA applicant’s interpretation of the scope of the patent would be inconsistent with the Agency’s longstanding ministerial role in patent-related matters. These comments suggest that FDA lacks the expertise to assess the adequacy of use codes and determine whether deference to the 505(b)(2) or ANDA applicant’s interpretation of the scope of the patent is justified. A fourth comment suggests that FDA provide an administrative appeals process and Administrative Law Judge review where FDA reviews a proposed labeling carve-out for a 505(b)(2) application or ANDA with deference to the 505(b)(2) or ANDA applicant’s interpretation of the scope of the patent. This comment also suggests that FDA avoid a “mere ministerial approach.”

(Response 24) As noted in Response 23, we are not finalizing this proposal at this time. Accordingly, we do not need to address comments regarding specific aspects of implementation of this proposal in this final rule.

(Comment 25) One comment recommends that FDA require an NDA holder to respond to a request to confirm the accuracy or relevance of patent information in 15 days, rather than 30 days. The comment maintains that a 15-day timeframe is consistent with the regulatory timeframe to make corrections to an incomplete or otherwise inadequate submission of patent information (see § 314.53(c)(2)(ii)).

(Response 25) We decline to modify the regulation as requested. We believe that a period of 30 days from the date on which FDA sends the statement of dispute to the NDA holder provides an appropriate opportunity for the NDA holder to consider the statement of dispute and submit a response that addresses the requirements of § 314.53(f)(1)(i).

(Comment 26) Two comments recommend that FDA clarify that an NDA holder's amendment to the use code in response to a patent listing dispute will not be considered untimely filed patent information under §§ 314.50(i)(4) and 314.94(a)(12)(vi). One comment expresses concern that whether and how an NDA holder responds to a method-of-use patent listing dispute may affect the availability of a 30-month stay should the NDA holder subsequently file a patent infringement action in response to notice of a paragraph IV certification to the patent.

(Response 26) We agree that an NDA holder's amendment to its use code or related information on Form FDA 3542 in response to a patent listing dispute should not be considered untimely filed patent information if it is submitted within 30 days of FDA's request under § 314.53(f)(1)(i)(B) and contains the information required under § 314.53(f)(1)(i)(B)(1) or (2) (see §§ 314.50(i)(4)(i) and 314.94(a)(12)(vi)(A) (describing untimely filing of patent information

“except as provided in § 314.53(f)(1)”). We note, however, that if an NDA holder responds to the patent listing dispute with an amendment to its use code more than 30 days after the date on which FDA sends the statement of dispute to the NDA holder, FDA will consider the amendment to be untimely filing of patent information because the submission does not comply with the requirements of § 314.53(f)(1).

The patent listing dispute procedure would not have an impact on the availability of a 30-month stay if other statutory and regulatory criteria are met (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act and § 314.107).

V.B.4.b. Requests by NDA holder (§ 314.53(f)(2)). We proposed to expressly require that if an NDA holder determines that a patent or patent claim (e.g., a method-of-use claim) no longer meets the statutory requirements for listing, the NDA holder must promptly notify FDA to withdraw the patent or patent information and request that the patent or patent information be removed from the list (see proposed § 314.53(f)(2)(i) and section 505(b)(1) and (c)(2) of the FD&C Act). If an NDA holder is required by court order to amend patent information or withdraw a patent from the list, we proposed to require the NDA holder to submit a copy of the court order to the Orange Book Staff within 14 calendar days of the date on which the order was entered. We also proposed to codify our current practice of removing a patent or patent information from the Orange Book when the NDA holder has informed us that the patent no longer meets the statutory requirements for listing if there is no first applicant eligible for 180-day exclusivity or upon the expiration of the 180-day exclusivity period (see proposed § 314.53(f)(2)(i)). In addition, we proposed that if the term of the patent is extended under the patent term restoration provisions of 35 U.S.C. 156, the NDA holder must submit a correction to the patent expiration date on Form FDA 3542 within 30 calendar days of receipt of a certificate

of extension or documentation of an extension of the term of the patent (see proposed § 314.53(f)(2)(ii) and 35 U.S.C. 156(e)(1) and (2)).

We proposed to require that corrections or changes to previously submitted patent information must be submitted on Form FDA 3542a or 3542, as appropriate (see proposed § 314.53(f)(2)(iii)). However, we proposed to clarify that an NDA holder's withdrawal of a patent and request to remove a patent from the list is not required to be submitted on Form FDA 3542, but the request must specify the patent number, the application number, and each product(s) approved in the application to which the request applies (see proposed § 314.53(f)(2)(iv)).

In the following paragraphs, we discuss two comments on these proposed provisions. After considering these comments, we are making clarifying revisions to the description of the required amendment or supplement and the address to which the amendment or supplement must be submitted, and technical amendments described in sections V.B.2.c and V.P.3 We are also revising proposed § 314.53(f)(2)(i) to more precisely describe our practice of removing a patent or patent information from the list in response to an NDA holder's request if there is no first applicant eligible for 180-day exclusivity based on a paragraph IV certification to that patent or after the 180-day exclusivity period of a first applicant based on that patent has expired or has been extinguished.

(Comment 27) Two comments request that FDA clarify the implications of failing to timely amend patent information or withdraw a patent. One of the comments requests that FDA clarify the meaning of "promptly notify FDA" in proposed § 314.53(f)(2)(i), and explain whether the timeframe may differ based on the circumstances (e.g., delay withdrawal of an original patent held invalid until the reissued patent has issued). The other comment suggests that if the NDA



holder fails to timely notify FDA of a patent term extension or of a court order to amend patent information or withdraw a patent from the list, the patent should be considered untimely filed.

(Response 27) FDA is establishing regulatory timeframes for withdrawal or amendment of patent information and withdrawal of a patent to promote the NDA holder's timely compliance with obligations under the FD&C Act and applicable regulations. If the NDA holder determines that a patent or patent claim no longer meets the statutory requirements for listing, the NDA holder must "promptly notify FDA" to withdraw the patent or patent information or amend the patent information to ensure that pending 505(b)(2) applications or ANDAs that contain a patent certification to the amended or withdrawn patent or patent information are not inappropriately delayed if they are otherwise eligible for approval. An NDA holder's withdrawal or amendment of patent information or withdrawal of the patent within 14 days of the date on which the NDA holder determines that the patent or patent claim no longer meets the requirements for listing under section 505(b)(1) or (c)(2) of the FD&C Act would be considered "prompt." If a court enters a final decision from which no appeal has been or can be taken that a patent is invalid, the NDA holder must promptly notify FDA to withdraw the patent and request that the patent be removed from the list irrespective of whether the NDA holder or patent owner is separately requesting a reissue of the patent.

We decline to modify the regulation to consider a patent untimely filed if the NDA holder fails to notify FDA of a court order to amend or withdraw patent information within 14 days because a court can enforce a failure to comply with its order. We also decline to modify the regulation to consider a patent untimely filed if the NDA holder fails to notify FDA of a patent term extension within 30 days because NDA holders have adequate incentive to inform FDA of any patent term extension. We require NDA holders to submit on Form FDA 3542 a correction

to the expiration date of the listed patent if the term is extended under 35 U.S.C. 156(e) to ensure that prospective 505(b)(2) and ANDA applicants have timely notice of changes to the asserted patent coverage for a listed drug.

(Comment 28) One comment recommends that FDA clarify where an NDA holder should send a voluntary request to remove patent information from the list.

(Response 28) We agree. We are revising § 314.53(f)(2)(iv) to clarify that the NDA holder must submit an amendment to its NDA to the same addresses described in § 314.53(d)(4)(ii) to promptly notify FDA to withdraw a patent and request that FDA remove a patent from the list. We are also revising § 314.53(f)(2)(i) and (iii) to clarify that an NDA holder must submit a copy of a court order to amend patent information or withdraw a patent from the list in an amendment to its NDA that bears the identification described in § 314.53(d)(6) (“Time Sensitive Patent Information”). In addition, we are changing the address for submission of the amendment from the Orange Book Staff to the CDER Central Document Room, consistent with § 314.53(d)(4)(ii).

#### V.C. Patent Certification (§§ 314.50(i) and 314.94(a)(12))

##### V.C.1. Method-of-Use Patents (§§ 314.50(i)(1)(iii) and 314.94(a)(12)(iii))

We proposed to revise §§ 314.50(i)(1)(iii) and 314.94(a)(12)(iii) to clarify that a 505(b)(2) or ANDA applicant that is not seeking approval for a condition of use other than an indication (e.g., a dosing regimen) that is covered by a method-of-use patent for the listed drug(s) relied upon or RLD, respectively, may submit a statement under section 505(b)(2)(B) or 505(j)(2)(A)(viii) of the FD&C Act, instead of a patent certification with respect to any such method-of-use claims.

We received no comments regarding this proposed revision. We are finalizing proposed §§ 314.50(i)(1)(iii) and 314.94(a)(12)(iii) with technical amendments to reflect the claim-based approach to patent certification requirements for patents that include a method-of-use claim (i.e., a 505(b)(2) or ANDA applicant may submit a statement with respect to one or more method-of-use claims and a paragraph IV certification with respect to the remaining patent claims). As revised, a statement under section 505(b)(2)(B) or 505(j)(2)(A)(viii) of the FD&C Act may be submitted if the applicant is not seeking approval for “an” indication or other condition of use claimed by a method-of-use patent rather than “any” indications or other conditions of use claimed by the method-of-use patent (see §§ 314.50(i)(1)(iii) and 314.94(a)(12)(iii)).

We also are making technical amendments throughout part 314 to clarify that a 505(b)(2) or ANDA applicant may submit an appropriate patent certification or statement (see, e.g., §§ 314.50(i)(1)(i)(A) through (C), (i)(5), (i)(6), (i)(6)(ii), (i)(6)(iii)(A)(1) and (2); 314.53(d)(3); and 314.94(a)(12)(i)(A) and (B), (a)(12)(vii) and (viii), (a)(12)(viii)(B), and (a)(12)(viii)(C)(1)(i) and (ii)).

#### V.C.2. Method-of-Manufacturing Patents (Deletion of §§ 314.50(i)(2) and 314.94(a)(12)(iv))

We proposed to remove §§ 314.50(i)(2) and 314.94(a)(12)(iv), which provide that an applicant is not required to make a certification with respect to any patent that claims only a method of manufacturing the drug product (method-of-manufacturing patent or process patent) for which the applicant is seeking approval. We proposed this deletion for clarity and consistency with the regulation that prohibits an NDA holder from submitting information on a patent that only claims a method of manufacturing the drug product (see § 314.53(b)).

In the following paragraphs, we discuss a comment on this proposed deletion. After considering this comment, we are removing (and reserving) §§ 314.50(i)(2) and 314.94(a)(12)(iv).

(Comment 29) One comment recommends that FDA permit the listing of process patents that claim production of the active pharmaceutical ingredient in the approved drug product (e.g., synthesis process or impurity reduction process).

(Response 29) We decline to adopt the suggestion provided in the comment. The FD&C Act requires an NDA applicant or holder to submit information on any patent that claims the drug or that claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug (see section 505(b)(1) and (c)(2) of the FD&C Act). A method-of-manufacturing patent or process patent does not meet the statutory requirement for listing because it does not claim an approved drug or an approved method of using the drug. We note, however, that a product-by-process patent is eligible for listing in the Orange Book because the invention claimed by the patent is, for example, the novel drug product and not the process used to make the product (see 68 FR 36676 at 36679 to 36680).

#### V.C.3. Licensing Agreement (§§ 314.50(i)(3) and 314.94(a)(12)(v))

We proposed to revise § 314.50(i)(3) regarding licensing agreements to remove the references to an “immediate effective date” and clarify that the patent owner with whom the applicant has a licensing agreement may consent to approval of the 505(b)(2) application (if otherwise justified) as of a specific date. We explained that this proposed revision did not alter the current requirements for a 505(b)(2) (or ANDA) applicant to submit a paragraph IV certification to a patent that claims the listed drug relied upon even though the applicant has a

licensing agreement with the patent owner (see proposed §§ 314.50(i)(3) and 314.94(a)(12)(v)).

We further explained that an applicant that has a licensing agreement with the patent owner would still be required to send notice of the paragraph IV certification to the NDA holder and each patent owner.

In the following paragraphs, we discuss a comment on this proposed revision. After considering this comment, we are making a clarifying revision and editorial corrections to § 314.50(i)(3) and conforming revisions to § 314.94(a)(12)(v).

(Comment 30) One comment requests that FDA revise § 314.50(i)(3) to apply to an “agreement” between a 505(b)(2) applicant and the patent owner(s), rather than restrict the provision to a “licensing agreement.” The comment maintains that other forms of agreement (e.g., a covenant not to sue) should not be treated differently for purposes of determining the earliest date agreed upon by the applicant and relevant patent owner(s) for approving an application. The comment also recommends that FDA amend § 314.94(a)(12)(v) to expressly describe consent to approval as of a specific date because the provision also should apply to ANDAs.

(Response 30) We decline to modify § 314.50(i)(3) to broadly refer to an agreement between a 505(b)(2) applicant and the patent owner. Licensing agreements are described in section 505(b)(1) and (c)(2) of the FD&C Act, which refer to a patent with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. It accords with the statute for a 505(b)(2) applicant to submit a paragraph IV certification based on a licensing agreement with the patent owner, and for the patent owner to consent to approval of the 505(b)(2) application as of a specific date (if the 505(b)(2) application is otherwise eligible for approval). However, it is

unclear whether other types of agreements (e.g., a covenant not to sue) would necessarily be consistent with a paragraph IV certification that the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the proposed product for which the 505(b)(2) application (or ANDA) is submitted. The FD&C Act does not contemplate FDA enforcement of private agreements between a 505(b)(2) (or ANDA) applicant and a patent owner that are unrelated to the statutory and regulatory requirements for approval.

As a practical matter, it is unnecessary to broaden this provision to describe other circumstances in which a patent owner may consent to approval as of a specific date. If a 505(b)(2) applicant submits a paragraph IV certification and the patent owner provides a covenant not to sue, then the patent owner would not initiate patent infringement litigation within the 45-day period and there would be no 30-month stay of approval. If a 505(b)(2) applicant changes a previously submitted certification or statement to a paragraph IV certification, the patent owner and NDA holder for the listed drug relied upon may waive their opportunity to file a patent infringement action within the 45-day period (see § 314.107(f)(3)).

We agree that the regulations should expressly provide that if an ANDA applicant has a licensing agreement with a patent owner, the patent owner may consent to approval of the ANDA as of a specific date (if the ANDA is otherwise eligible for approval). We are revising § 314.94(a)(12)(v) to describe the requirements for a written statement from the patent owner that has a licensing agreement with the applicant and consents to approval of the ANDA as of a specific date. Agreements between an ANDA applicant and a brand name drug company that must be filed with the Assistant Attorney General and the FTC are described in section 1112 of the MMA.

We also are revising §§ 314.50(i)(3) and 314.94(a)(12)(v) to clarify that the 505(b)(2) application or ANDA will be approved based on consent to approval as of a specific date only if the 505(b)(2) application or ANDA is “otherwise eligible for approval” rather than “otherwise justified.”

V.D. Notice of Paragraph IV Certification (§§ 314.52 and 314.95)

V.D.1. Timing of Notice

V.D.1.a. Date before which notice may not be given. We proposed to revise our regulations to clearly delineate the two limitations on the timeframe within which notice of a paragraph IV certification to a listed patent must be provided to the NDA holder and each patent owner: The date before which notice must not be given and, as discussed in section V.D.1.b, the date by which notice must be given.

We proposed to codify our longstanding policy that notice of a paragraph IV certification may not be sent by a 505(b)(2) or ANDA applicant unless and until we have notified the applicant that its application has been filed or received, as appropriate (see proposed §§ 314.52(b)(1) and 314.95(b)(1)). We proposed that any notice sent by a 505(b)(2) or ANDA applicant before the receipt of an acknowledgment letter or paragraph IV acknowledgment letter is invalid, and thus does not trigger either the 45-day period in which the NDA holder and each patent owner may initiate a patent infringement action and obtain a 30-month stay or the beginning of any related 30-month period. We proposed that an applicant that prematurely sends notice of a paragraph IV certification would be required to resend notice within the required timeframe after the 505(b)(2) application or ANDA has been filed or received, respectively, to satisfy the notice requirement of the FD&C Act and, in the case of a first applicant, to qualify for 180-day exclusivity (see proposed §§ 314.52(b)(2) and 314.95(b)(2)).

We proposed to clarify that if a 505(b)(2) or ANDA applicant submits an amendment containing a paragraph IV certification before the filing or receipt of the 505(b)(2) application or ANDA, respectively, the applicant would be required to wait until it has received an acknowledgment letter or a paragraph IV acknowledgment letter before sending notice of its paragraph IV certification to the NDA holder and each patent owner (see proposed §§ 314.52(b) and (d)(2) and 314.95(b) and (d)(2)).

With respect to patents that are listed in the Orange Book after submission of an ANDA, we proposed that any notice of paragraph IV certification would be invalid and would not be considered to comply with the notice requirement of the FD&C Act if it is sent before the first working day after the day the patent is listed in the Orange Book (see proposed §§ 314.94(a)(12)(viii)(C)(1)(ii) and 314.95(b)(2)). We proposed that the term “working day” would have the meaning provided in 21 CFR 1.377 (“any day from Monday through Friday, excluding Federal holidays”). We explained that this proposal is intended to discourage ANDA applicants from submitting a paragraph IV certification and sending notice to the NDA holder and each patent owner every day during the 30-day period after issuance of a patent that could be listed for the RLD in an effort to qualify as a first applicant eligible for 180-day exclusivity if such patent ultimately is listed for the RLD in the Orange Book. We also noted that this proposed requirement would ensure that all ANDA applicants (irrespective of time zone) have a reasonable opportunity to be first to certify to a newly listed patent.

In the following paragraphs, we discuss several comments on our proposed regulations regarding the date before which notice of paragraph IV certification must not be given. After considering these comments, we are revising § 314.52(b)(2) to provide that a 505(b)(2) applicant must send notice of a paragraph IV certification on or after the date of filing of the 505(b)(2)



application described in § 314.101(a)(2) or (3), as applicable, rather than on or after the date it receives a paragraph IV acknowledgment letter. We are revising proposed § 314.95(b)(2) to delete the reference to an “acknowledgment letter” because an ANDA applicant will now receive a “paragraph IV acknowledgment letter” if it amends its ANDA to add a paragraph IV certification before the ANDA is received (see section V.A.1).

(Comment 31) One comment asserts that the statutory terms “submits” and “files” in section 505(j)(2)(B)(ii)(I) and (II) of the FD&C Act, respectively, indicate that an ANDA applicant may send notice of a paragraph IV certification at the time of submission of an amendment to an ANDA containing a paragraph IV certification, even if the ANDA has not yet been “filed” (i.e., “received” under § 314.101(b)). The comment suggests that ANDA applicants that submit an amendment containing the first paragraph IV certification to a patent listed for the RLD are concerned that they may risk eligibility for 180-day exclusivity if they do not send notice at the time of submission of the amendment, even though the ANDA has not been received under § 314.101(b). The comment proposes that FDA allow ANDA applicants to “change” rather than “amend” their patent certification in an amendment prior to filing, and consider the date of the “change” for purposes of determining eligibility for 180-day exclusivity.

(Response 31) We disagree with the comment’s interpretation of section 505(j)(2)(B)(ii)(II) of the FD&C Act, and decline to adopt the comment’s proposed revision to the regulations governing submission of a paragraph IV certification prior to receipt of the ANDA.

As a preliminary matter, we note that the requirement that an ANDA applicant must wait until its ANDA has been received before sending notice of a paragraph IV certification ensures that the NDA holder and patent owner do not needlessly expend resources to initiate litigation

with respect to an ANDA that is incomplete and therefore may not be reviewed by the Agency (see “Abbreviated New Drug Application Regulations,” 54 FR 28872 at 28887, July 10, 1989; see also 59 FR 50338 at 50349 to 50350). This reflects the Agency’s view that Congress did not intend for incomplete ANDA submissions to have the potential to trigger legal action by an NDA holder or patent owner (see 54 FR 28872 at 28887; see also Allergan, Inc. v. Actavis, Inc., 2014 WL 7336692 at \*12 (E.D. Tex. 2014) (finding that the act of infringement created by 35 U.S.C. 271(e)(2) requires that the ANDA has been received by FDA, not merely transmitted to FDA). Accordingly, our existing regulations require that an ANDA applicant’s notice of a paragraph IV certification must include a statement that FDA has received the ANDA (see § 314.95(c)(1)).

The requirement that notice of a paragraph IV certification only be sent after FDA has received the ANDA was ratified by the MMA, which established a 20-day period for sending notice of a paragraph IV certification that runs from the date of the postmark on the notice with which FDA informs the applicant that the ANDA has been filed (i.e., received under § 314.101(b)) (see section 505(j)(2)(B)(ii)(I) of the FD&C Act and section V.D.1.b). The MMA also requires that an ANDA applicant send notice of a paragraph IV certification submitted in an amendment or supplement to the ANDA at the time of submission of the amendment or supplement, regardless of whether the applicant already has given notice with respect to another paragraph IV certification contained in the ANDA or in an amendment or supplement to the ANDA (see section 505(j)(2)(B)(ii)(II) of the FD&C Act). Consistent with the framework established by section 505(j)(2)(B)(ii) of the FD&C Act, FDA interprets section 505(j)(2)(B)(ii)(II) of the FD&C Act to apply only to an amendment to the ANDA that is submitted after the Agency has received the ANDA (see SB Pharmco Puerto Rico, Inc. v. Mutual Pharmaceutical Co., 552 F. Supp. 2d 500, 510 (E.D. Pa.), appeal dismissed, 2008 U.S. App.

LEXIS 27672 (Fed. Cir. 2008) (upholding FDA’s interpretation of section 505(j)(2)(B)(ii)(II) of the FD&C Act and finding that notice of a paragraph IV certification sent at the time of submission of an amendment to an ANDA that had not yet been received “was not valid or timely”). Thus, we disagree with the comment’s suggestion that an ANDA applicant can submit an amendment containing a paragraph IV certification before the ANDA is received and immediately send notice of the paragraph IV certification. If an ANDA applicant submits an amendment containing a paragraph IV certification before it has received a paragraph IV acknowledgment letter advising that the ANDA has been received for substantive review, the applicant is required to send notice of its paragraph IV certification within 20 days after the date of the postmark on the paragraph IV acknowledgment letter.

Based on the Agency’s interpretation of the statute, it is unnecessary to use the terminology suggested in the comment to describe an amendment that contains a paragraph IV certification to a newly listed patent or that changes a previously submitted patent certification or statement to a paragraph IV certification and is submitted before receipt of the ANDA.

The relevant date for determining eligibility for 180-day exclusivity based upon submission of a paragraph IV certification contained in an amendment is the date of submission of the amendment. We are revising § 314.95(d)(2) to clarify that if an ANDA applicant’s notice of paragraph IV certification is timely provided in accordance with § 314.95(b)(2) and the applicant has not submitted a previous paragraph IV certification, FDA will base its determination of whether the applicant is a first applicant on the date of submission of the amendment containing the paragraph IV certification.

(Comment 32) One comment accepts FDA’s “settled administrative practice” that a 505(b)(2) or ANDA applicant may not send notice of paragraph IV certification until the

application is accepted for review, but contends that FDA may not condition a 505(b)(2) applicant's ability to send notice on its prior receipt of a paragraph IV acknowledgment letter that would be sent up to 14 days after the 505(b)(2) application is accepted for review (filed). The comment maintains that the benefits of this approach have not been shown to outweigh the costs of a potential 2-week delay in approval of a 505(b)(2) application, and that the proposal is inconsistent with the statute. Another comment recommends that FDA send a paragraph IV acknowledgment letter to a 505(b)(2) applicant via email on the date on which the 505(b)(2) application is filed to eliminate the disparity between the dates on which paragraph IV acknowledgment letters are sent to 505(b)(2) and ANDA applicants. A third comment requests that FDA clarify when an ANDA applicant can send notice if the paragraph IV acknowledgment letter is not received on day 60.

(Response 32) We agree that there should not be a delay of approximately 2 weeks between the date on which a 505(b)(2) application is filed and the date on or after which a 505(b)(2) applicant must send notice of a paragraph IV certification to the NDA holder and each patent owner. We are revising proposed § 314.52(b)(1) and (2) to provide that a 505(b)(2) applicant must send notice of a paragraph IV certification on or after the date of filing of the 505(b)(2) application described in § 314.101(a)(2) or (3), as applicable, rather than on or after the date it receives a paragraph IV acknowledgment letter, and we are making conforming revisions to § 314.52(d)(1) and (2). This revised approach ensures that notice of a paragraph IV certification will not be sent before the Agency has filed the relevant 505(b)(2) application, and avoids a delay of up to 2 weeks in the potential initiation of patent infringement litigation by an NDA holder or patent owner and any corresponding 30-month stay of approval of the 505(b)(2) application.

FDA determines whether a 505(b)(2) application may be filed within 60 days after FDA is in receipt of the 505(b)(2) application (see § 314.101(a)(1)). If the 505(b)(2) applicant does not receive a refusal to file letter on or before day 60, the 505(b)(2) application is deemed filed. If FDA refuses to file the 505(b)(2) application and the 505(b)(2) application is filed over protest or resubmitted, then the date of filing described in § 314.101(a)(3) applies. We are requiring that a 505(b)(2) applicant send notice of a paragraph IV certification on or after the date of filing of the 505(b)(2) application, but not later than 20 days after the date of the postmark on the paragraph IV acknowledgment letter (see § 314.52(b)(1)). The “paragraph IV acknowledgment letter” for a 505(b)(2) application is the filing communication that generally is sent to the 505(b)(2) applicant not later than 14 calendar days after the 60-day filing date (sometimes referred to as the “74 day letter”) (see section V.A.1). The “date of the postmark” for a paragraph IV acknowledgment letter for a 505(b)(2) application is considered to be four calendar days after the date on which the letter is signed by the signatory authority (generally the Division Director or designee in the OND review division). Accordingly, this revision to our regulations implements the statutory requirement that notice be sent within 20 days of the postmark on the filing communication while preserving the principle that notice must not be sent before a 505(b)(2) application is filed.

We are maintaining the requirement that an ANDA applicant must send notice of a paragraph IV certification on or after the date it receives a paragraph IV acknowledgment letter because FDA intends to electronically transmit the letter to the ANDA applicant on the date on which the ANDA is received under § 314.101(b). Accordingly, in contrast to the interval of up to 14 days for 505(b)(2) applications, there is no interval between the date on which the ANDA is received under § 314.101(b) and the date on which an ANDA applicant receives a paragraph

IV acknowledgment letter (see section V.A.6). An ANDA applicant can send notice of a paragraph IV certification submitted in an original ANDA or submitted in an amendment to an ANDA that has not yet been received on or after the date the ANDA applicant receives a paragraph IV acknowledgment letter.

(Comment 33) One comment asserts that the proposed requirement that a paragraph IV certification must not be submitted earlier than the first working day after the day the patent or patent claim is listed in the Orange Book would conflict with the statute and prevent ANDA applicants from submitting a paragraph IV certification to a newly listed patent at the first lawful opportunity. Another comment maintains that the proposed requirement for submission of a paragraph IV certification to a newly listed patent may result in multiple ANDA applicants becoming eligible for 180-day exclusivity and thus would dilute the value of 180-day exclusivity.

(Response 33) We believe that our approach to patent certification requirements for newly listed patents is consistent with the statute and provides a reasonable opportunity for ANDA applicants to compete to have the first substantially complete ANDA that contains a paragraph IV certification to a listed patent for the RLD.

The requirement that an ANDA applicant must not submit a paragraph IV certification earlier than the first working day after the day the patent or patent claim is listed in the Orange Book reflects FDA's determination that selecting the first working day after the day on which the patent information is published creates a level playing field for all ANDA applicants (see §§ 314.94(a)(12)(viii)(C)(1)(ii) and 314.95(b)(2)). One court has determined, in the absence of a regulation to the contrary, that "reality matters" if a patent has been submitted to FDA, and an ANDA applicant can submit a paragraph IV certification even if the patent is not yet listed in the

Orange Book (see Teva Pharms., USA, Inc. v. Leavitt, 548 F.3d 103, 105 (D.C. Cir. 2008)).

However, FDA has determined that permitting serial submissions of amendments and multiple notices of paragraph IV certifications is overly burdensome to FDA and NDA holders. Such a practice makes it difficult to determine which paragraph IV certification and notice of paragraph IV certification is valid. Our decision to level the playing field for paragraph IV certifications in this manner is consistent with our authority to establish rules for the efficient enforcement of the FD&C Act (see section 701(a) of the FD&C Act).

We are not persuaded by the comment's assertion that leveling the playing field for ANDA applicants will dilute the value of 180-day exclusivity. For example, FDA continues to receive multiple ANDAs on the day that 4 years of a 5-year exclusivity period under section 505(j)(5)(F)(ii) of the FD&C Act has expired (the first day that ANDAs containing a paragraph IV certification are permitted to be submitted) even though many of these ANDAs will likely share eligibility for 180-day exclusivity.

(Comment 34) One comment supports the proposed requirement that a paragraph IV certification must not be submitted earlier than the first working day after the day the patent or patent claim is listed in the Orange Book, but recommends that FDA establish a time after which patent information listed in the Orange Book will be deemed to have been published the next day. Another comment suggests that FDA instantaneously notify ANDA applicants when a patent is listed for the RLD after ANDA submission to provide an equal opportunity for timely submission of an appropriate patent certification or statement to the pending ANDA and, if applicable, notice of paragraph IV certification.

(Response 34) We decline to adopt the suggestions provided in the comments. FDA generally posts daily electronic updates to the Orange Book in the afternoon (Eastern Standard

Time); however, we are not establishing a specific time by which FDA will update the Orange Book to preserve flexibility in the event of technical difficulties. Applicants will have an equal opportunity for timely submission of an appropriate patent certification or statement for a newly listed patent or patent claim because FDA will make this information publicly available through the Orange Book. Although we decline to undertake the burden of notifying individual ANDA applicants when a patent or patent claim for the RLD is newly listed in the Orange Book, we are committed to facilitating public access to the Orange Book through efficient means (see, e.g., the “Orange Book Express” mobile application launched on November 9, 2015).

V.D.1.b. Date by which notice must be given. We proposed to establish a regulation that would implement section 505(b)(3)(B) and (j)(2)(B)(ii) of the FD&C Act by providing that an applicant must send notice of a paragraph IV certification contained in a 505(b)(2) application or ANDA not later than 20 days after the date of the “postmark” on the acknowledgment letter or paragraph IV acknowledgment letter (see proposed §§ 314.52(b)(1) and 314.95(b)(1) and section 505(b)(3)(B)(i) and (j)(2)(B)(ii)(I) of the FD&C Act). We proposed a definition of the term “postmark” and, as applied to paragraph IV acknowledgment letters for 505(b)(2) applications, an alternate proposed interpretation of the term “postmark” to reflect current practice regarding the mailing of filing communications (see section V.A.1). We also proposed to specify the method of calculating the 20-day period for providing notice of a paragraph IV certification (see proposed §§ 314.52(b)(1) and 314.95(b)(1)).

We proposed that an applicant must send notice of a paragraph IV certification contained in an amendment to a 505(b)(2) application or ANDA that has been filed or received for substantive review, respectively, or in a supplement to an approved 505(b)(2) application or ANDA at the same time that the amendment or supplement is submitted to FDA (see proposed



§§ 314.52(d)(1) and 314.95(d)(1) and section 505(b)(3)(B)(ii) and (j)(2)(B)(ii)(II) of the FD&C Act). We proposed that notice of a paragraph IV certification in an amendment or supplement must be provided regardless of whether the applicant has already given notice with respect to another paragraph IV certification contained in the 505(b)(2) application or ANDA or in an amendment or supplement to the 505(b)(2) application or ANDA (see proposed §§ 314.52(d)(1) and 314.95(d)(1) and section 505(b)(3)(B)(ii) and (j)(2)(B)(ii)(II) of the FD&C Act).

We proposed to require an applicant that submits an amendment or supplement to a 505(b)(2) application or ANDA that seeks approval for a different strength of the drug product and contains a paragraph IV certification adhere to the timing requirements for notice in §§ 314.52(d)(1) or (2) and 314.95(d)(1) or (2), respectively, based on whether the 505(b)(2) application has been filed or the ANDA has been received (see proposed §§ 314.52(d)(3) and 314.95(d)(3)).

We did not receive any other comments on proposed §§ 314.52(b)(1), (d)(1) and (2), and 314.95(b)(1), (d)(1) and (2). We are finalizing proposed § 314.52(b)(1) and (2) and (d)(1) and (2) with the revisions discussed in Response 32. We are finalizing proposed § 314.95(b)(1) and (d)(2) with clarifying revisions to consistently refer to “a paragraph IV acknowledgment letter” because these provisions refer to an ANDA that contains a paragraph IV certification before the ANDA is received and thus FDA will send the ANDA applicant a paragraph IV acknowledgment letter. We also are making the clarifying revision to proposed § 314.95(d)(2) discussed in Response 31. We are finalizing proposed § 314.95(d)(1) with a clarifying revision to add the phrase “or an acknowledgment letter” because an applicant may amend or supplement its ANDA to include a paragraph IV certification irrespective of whether the ANDA contained a

paragraph IV certification at the time of receipt. We also are making the technical amendment to § 314.95(d)(1) described in section V.P.1.

#### V.D.2. Contents of Notice

We proposed that a 505(b)(2) or ANDA applicant's notice of a paragraph IV certification must include, among other things: (1) A statement that data from any required bioavailability or bioequivalence studies have been submitted; (2) a statement that the applicant has received an acknowledgment letter or a paragraph IV acknowledgment letter for its 505(b)(2) application or ANDA; (3) the patent number and expiration date of each patent listed in the Orange Book that is the subject of the paragraph IV certification; and (4) an offer of confidential access, if the applicant alleges that the patent will not be infringed and may later decide to file a civil action for declaratory judgment in accordance with section 505(c)(3)(D) and (j)(5)(C) of the FD&C Act) (see proposed §§ 314.52(c) and 314.95(c)). We also proposed to require the 505(b)(2) or ANDA applicant to cite section 505(b)(3)(D) and (j)(2)(B)(iv) of the FD&C Act, respectively, as amended by the MMA, in the notice of paragraph IV certification (see proposed §§ 314.52(c) and 314.95(c)). In the proposed rule, we explained that the Agency assesses neither the adequacy of the contents of a 505(b)(2) or ANDA applicant's notice of paragraph IV certification nor the applicant's stated basis for certifying that a listed patent is invalid, unenforceable, or will not be infringed by its proposed drug product.

In the following paragraphs, we discuss two comments on the proposed requirements for the content of a notice of paragraph IV certification. After considering these comments, we are not finalizing proposed § 314.52(c)(3) and we are making conforming editorial changes to the numbering of subsequent paragraphs in § 314.52(c). We are revising proposed § 314.95(c)(3) to omit the reference to an "acknowledgment letter" and require that the ANDA applicant include a

statement that the applicant has received the paragraph IV acknowledgment letter for the ANDA. We are making a grammatical correction to the introductory text of §§ 314.52(c) and 314.95(c) to provide that the notice must include, but is not limited to, the information described in §§ 314.52(c)(1) through (8) and 314.95(c)(1) through (9). We are finalizing the remaining provisions of proposed §§ 314.52(c) and 314.95(c) without change, except for a revision to proposed §§ 314.52(c)(8) and 314.95(c)(8) to clarify that an offer of confidential access must be provided by an applicant that seeks to preserve the option to file a civil action for declaratory judgment in accordance with section 505(c)(3)(D) or (j)(5)(C) of the FD&C Act.

(Comment 35) One comment asserts that FDA lacks authority to require a 505(b)(2) or ANDA applicant to include, in any notice of paragraph IV certification, a statement that the applicant has received an acknowledgment letter or a paragraph IV acknowledgment letter because section 505(b)(3)(D) and (j)(2)(B)(iv) of the FD&C Act does not expressly require such a statement.

(Response 35) We disagree. FDA has the authority to establish regulations regarding the contents of notice of a paragraph IV certification to support the efficient enforcement of the FD&C Act (see section 701(a) of the FD&C Act). The FD&C Act requires that a notice of paragraph IV certification must state that the 505(b)(2) application or ANDA containing the certification “has been submitted” (see section 505(b)(3)(D)(i) and (j)(2)(B)(iv)(I) of the FD&C Act). As discussed in Response 31, it is the Agency’s longstanding policy that notice of a paragraph IV certification may not be sent unless and until we have notified the applicant that its 505(b)(2) application has been filed or its ANDA has been received because premature notice could result in lawsuits over applications that FDA refuses to file or receive and thus no longer are pending. Accordingly, our existing regulations require that a 505(b)(2) or ANDA applicant’s

notice of a paragraph IV certification must include a statement that FDA has filed the NDA (in the case of a 505(b)(2) application) or has received the ANDA (see §§ 314.52(c)(1) and 314.95(c)(1)). To help ensure that notices of paragraph IV certifications are not sent prematurely, we also are requiring that an ANDA applicant's notice of paragraph IV certification include a statement that the applicant has received the paragraph IV acknowledgment letter for the ANDA (see § 314.95(c)(3)). We are revising proposed § 314.95(c)(3) to delete the reference to an "acknowledgment letter" because an ANDA applicant will now receive a "paragraph IV acknowledgment letter" if the ANDA contains a paragraph IV certification at any time before the ANDA is received (see section V.A.1).

With respect to a 505(b)(2) application, we are maintaining the requirement that a 505(b)(2) applicant's notice of a paragraph IV certification must include a statement that FDA has filed the NDA (see § 314.52(c)(1)). However, we are not requiring the 505(b)(2) applicant to include a statement that it has received a paragraph IV acknowledgment letter because we are revising our regulations to provide that a 505(b)(2) applicant must send notice of a paragraph IV certification on or after the date of filing of the 505(b)(2) application described in § 314.101(a)(2) or (3), as applicable, rather than on or after the date the applicant receives a paragraph IV acknowledgment letter (see § 314.52(b)(1) and Response 32).

(Comment 36) One comment requests that FDA revise the regulations to enable any recipient of notice of paragraph IV certification to request that FDA confirm the adequacy of notice with respect to statutory and regulatory requirements (other than the factual and legal basis for the paragraph IV certification). This comment recommends that FDA provide that inadequate notice is invalid and does not trigger the 45-day period described in section 505(c)(3)(C) or (j)(5)(B)(iii) of the FD&C Act. Another comment recommends that FDA

provide an additional time period in which a 505(b)(2) or ANDA applicant can correct a deficient notice of paragraph IV certification that would extend the time for a patent holder under its duties or obligations.

(Response 36) We decline to revise the regulations to provide for a ministerial review of notice of a paragraph IV certification to evaluate compliance with the statutory and regulatory requirements. A 505(b)(2) or ANDA applicant is required to submit an amendment to its 505(b)(2) application or ANDA certifying, among other things, that the notice of paragraph IV certification met the content requirements under §§ 314.52(c) or 314.95(c), respectively (see §§ 314.52(b)(3) or 314.95(b)(3)). The regulations also provide that a copy of the notice of paragraph IV certification does not need to be submitted to FDA (see §§ 314.52(b)(3) or 314.95(b)(3)). Given the clarifying revisions to the regulations to enhance compliance with the requirements for notice of a paragraph IV certification and the administrative burden that would be associated with a ministerial review of a notice of paragraph IV certification, we do not believe that such review is warranted. The second comment does not clearly describe the requested action or provide adequate support for any proposed change. We note, however, that an applicant may amend its 505(b)(2) application or ANDA with a written statement that a later date should be used as the first day of the 45-day period provided in section 505(c)(3)(C) or (j)(5)(B)(iii) of the FD&C Act (see §§ 314.52(f) and 314.95(f)).

#### V.D.3. Documentation of Timely Sending and Receipt of Notice

V.D.3.a. Acceptable methods of sending notice of paragraph IV certification. We proposed to expand the list of acceptable delivery methods that 505(b)(2) and ANDA applicants may use to send notice of paragraph IV certification to the NDA holder and each patent owner by permitting a 505(b)(2) or ANDA applicant to use a “designated delivery service” (see

proposed §§ 314.52(a) and 314.95(a)). We proposed to define a “designated delivery service” to mean a delivery service provided by a trade or business that FDA determines: (1) Is available to the general public throughout the United States; (2) records electronically to its database, kept in the regular course of its business, or marks on the cover in which any item referred to in this section is to be delivered, the date on which the item was given to the trade or business for delivery; and (3) provides overnight or 2-day delivery service throughout the United States (see §§ 314.52(g)(1) and 314.95(g)(1)). We proposed to periodically issue guidance describing designated delivery services that meet the regulatory criteria (see proposed §§ 314.52(g)(2) and 314.95(g)(2)). We also proposed to clarify that a 505(b)(2) or ANDA applicant may send notice of paragraph IV certification by an alternative method (i.e., a method other than registered or certified mail, return receipt requested, or a designated delivery service) only if FDA has agreed in advance that the method will produce an acceptable form of documentation (see proposed §§ 314.52(a)(4) and (e) and 314.95(a)(4) and (e)).

In the following paragraphs, we discuss a comment on these proposed provisions. After considering this comment, we are finalizing proposed §§ 314.52(a) and (g)(1) and 314.95(a) and (g)(1) without change, except for a technical amendment to add “505(b)(2)” before “applicant” in § 314.52(a) for clarity. We are revising §§ 314.52(g)(2) and 314.95(g)(2) to clarify that FDA may periodically issue guidance regarding designated delivery services.

(Comment 37) One comment requests that FDA clarify whether a 505(b)(2) or ANDA applicant may use a delivery service that appears to satisfy the criteria in §§ 314.52(g)(1) and 314.95(g)(1) even if the delivery service has not been identified by FDA in periodic guidance.

(Response 37) At this time, FDA does not intend to identify specific designated delivery services in guidance. A 505(b)(2) or ANDA applicant that sends notice of a paragraph IV

certification may use a delivery service that satisfies the regulatory criteria in §§ 314.52(g)(1) or 314.95(g)(1), as applicable, without FDA's prior approval. For purposes of the definition of "designated delivery service," FDA is clarifying that "United States" means the 50 States, the District of Columbia, and the Commonwealth of Puerto Rico, but not the Territories. This approach acknowledges that some delivery services may not routinely provide overnight or 2-day delivery services to each of the Territories of the United States. If a 505(b)(2) or ANDA applicant is required to send notice of a paragraph IV certification to an NDA holder or patent owner (or its representative) that resides in a Territory of the United States or outside the United States, the applicant should ensure that the designated delivery service provides service to the area or request permission to use an alternate method of delivery.

We are revising §§ 314.52(g)(2) and 314.95(g)(2) to clarify that FDA may periodically issue guidance regarding designated delivery services. We note that a 505(b)(2) or ANDA applicant may send notice of a paragraph IV certification by an alternate method that does not meet the criteria in §§ 314.52(g)(1) or 314.95(g)(1) only if the applicant has obtained FDA's agreement in advance (see §§ 314.52(a)(4) and 314.95(a)(4)).

V.D.3.b. Amendment documenting timely sending and confirmation of receipt of notice of paragraph IV certification. We proposed to revise §§ 314.52(e) and 314.95(e) to clarify the requirements for submission of an amendment to a 505(b)(2) application or ANDA, respectively, containing documentation of timely sending of notice of paragraph IV certification and confirmation of receipt of same by the NDA holder and each patent owner.

We proposed that an applicant must amend its 505(b)(2) application or ANDA at the time that it provides notice of a paragraph IV certification with a statement certifying that notice has been provided to the NDA holder and each patent owner as required by §§ 314.52(a) and

314.95(a) and met the content requirements described in §§ 314.52(c) and 314.95(c) (see proposed §§ 314.52(b)(3) and 314.95(b)(3)). We also proposed to clarify that a copy of the notice of paragraph IV certification itself does not need to be submitted to FDA in the amendment (see proposed §§ 314.52(b)(3) and 314.95(b)(3)).

We proposed that an applicant must amend its 505(b)(2) application or ANDA with documentation that the notice of paragraph IV certification was sent on a date that complies with the timeframe required by § 314.52(b) or (d) or § 314.95(b) or (d), as applicable (see proposed §§ 314.52(e) and 314.95(e) and section 505(b)(3)(B) and (j)(2)(B)(ii) of the FD&C Act). For administrative efficiency, we proposed that a 505(b)(2) or ANDA applicant can submit a single amendment that contains documentation of timely sending of the notice(s) of paragraph IV certification and receipt of the notice(s) by each person provided the notice. We proposed that the amendment must be submitted within 30 days after the last date on which notice was received by a person described in § 314.52(a) or § 314.95(a), respectively (see proposed §§ 314.52(e) and 314.95(e)). We also proposed to clarify the types of documentation of timely sending and receipt of notice of paragraph IV certification that can satisfy the regulatory requirements (see proposed §§ 314.52(e) and 314.95(e)).

In addition, we proposed to require that ANDA applicants include in their amendment a dated printout of the Orange Book entry for the RLD that includes the patent that is the subject of the notice of paragraph IV certification. This proposed requirement would ensure that a paragraph IV certification that may qualify an ANDA applicant for 180-day exclusivity is submitted only for a listed patent and is not sent before the first working day after the day the patent is listed in the Orange Book (see proposed §§ 314.95(b)(2) and 314.94(a)(12)(viii)(C)(1)(ii)).



We did not receive any comments on these proposed revisions. However, for administrative efficiency, the Agency has revised §§ 314.52(b)(3) and 314.95(b)(3) to remove the requirement for a 505(b)(2) or ANDA applicant to submit an amendment at the time it sends notice of paragraph IV certification. Instead, the 505(b)(2) or ANDA applicant may submit a single amendment that contains the statements required by §§ 314.52(b)(3) and 314.95(b)(3) and documentation of timely sending and receipt of notice of paragraph IV certification if the amendment contains all of the information required by §§ 314.52(b)(3) and (e) and 314.95(b)(3) and (e) and is submitted within 30 days of the date on which the last notice was received.

V.E. Amended Patent Certifications (§§ 314.50(i)(6) and 314.94(a)(12)(viii))

We proposed to revise the introductory text of § 314.94(a)(12)(viii) to remove the provision that restricts an ANDA applicant from changing a paragraph IV certification to a paragraph III certification in certain circumstances. We also proposed to revise §§ 314.50(i)(6) and 314.94(a)(12)(viii) to require that a 505(b)(2) or ANDA applicant submit an amended patent certification as an amendment to its pending application (including a supplemental 505(b)(2) application or supplemental ANDA) and not by letter. We received no comments, and we are finalizing these proposed revisions to §§ 314.50(i)(6) and 314.94(a)(12)(viii) without change, except for the technical amendments described in sections V.P.2 and V.P.6.

V.E.1. Amended Patent Certifications After a Finding of Infringement

We proposed to amend §§ 314.50(i)(6)(i) and 314.94(a)(12)(viii)(A) to reflect changes to the FD&C Act made by the MMA that clarify the requirements for a 505(b)(2) or ANDA applicant to amend its paragraph IV certification after a judicial finding of patent infringement (see section 505(c)(3)(C)(ii)(II) and (j)(5)(B)(iii)(II)(bb) of the FD&C Act). We proposed to require that a 505(b)(2) and ANDA applicant submit an amendment to change its paragraph IV

certification to a paragraph III certification or, if appropriate, to a statement under section 505(b)(2)(B) or (j)(2)(A)(viii) of the FD&C Act if a court enters a final decision from which no appeal has been or can be taken that the patent at issue is valid and has been infringed (see proposed §§ 314.50(i)(6)(i) and 314.94(a)(12)(viii)(A)). We proposed to apply this requirement irrespective of whether the patent infringement action was brought within 45 days of receipt of the notice of paragraph IV certification because a 505(b)(2) or ANDA applicant can no longer lawfully maintain a paragraph IV certification after the final court decision.

We also proposed to require a 505(b)(2) or ANDA applicant to submit an amendment to change its paragraph IV certification to a paragraph III certification or, if appropriate, to a statement under section 505(b)(2)(B) or (j)(2)(A)(viii) of the FD&C Act if a court signs a settlement order, or consent decree in the action that includes a finding that the patent is infringed, unless the final decision, settlement order or consent decree also finds the patent to be invalid (see proposed §§ 314.50(i)(6)(i) and 314.94(a)(12)(viii)(A)). We noted, however, that if a settlement is reached without a finding of patent infringement or invalidity, then a paragraph IV certification may continue to be appropriate.

We received no comments, and we are finalizing these proposed revisions to §§ 314.50(i)(6)(i) and 314.94(a)(12)(viii)(A) without change, except for a technical amendment to clarify that a settlement order or consent decree must be signed and entered by the court as required by section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act and the additional technical amendments described in sections V.P.2 and V.P.6.

V.E.2. Amended Certifications After Request by the NDA Holder to Remove a Patent or Patent Information From the List

We proposed to revise §§ 314.50(i)(6)(ii) and 314.94(a)(12)(viii)(B) to clarify the circumstances and timeframe in which a 505(b)(2) or ANDA applicant must submit an amended patent certification to its 505(b)(2) application or ANDA after an NDA holder has requested removal of a patent or patent information from the list (patent delisting). These proposed revisions also describe our practice regarding patent delisting as it relates to the eligibility of one or more first applicants for 180-day exclusivity.

We received one comment supporting our proposal that if an NDA holder has requested removal of a patent or patent information from the list and one or more first applicants are eligible for 180-day exclusivity, FDA will not remove the patent or patent information from the list until we have determined that no first applicant is eligible for 180-day exclusivity or the 180-day exclusivity is extinguished (see proposed §§ 314.50(i)(6)(ii) and 314.94(a)(12)(viii)(B)). We are finalizing proposed §§ 314.50(i)(6)(ii) and 314.94(a)(12)(viii)(B) with revisions to consistently refer to a request to remove a patent or patent information from the Orange Book and to clarify that the patent or patent information will remain listed until any 180-day exclusivity based on that patent has expired or has been extinguished. We also are making the technical amendments described in sections V.P.1, V.P.3, and V.P.6 and the revision to § 314.94(a)(12)(viii)(B) described in section V.E.3.

#### V.E.3. Amended Certifications Upon Patent Reissuance

We proposed to revise our regulations to describe a 505(b)(2) and ANDA applicant's patent certification obligations with respect to a reissued patent. Our approach reflected our consideration of the original patent and the reissued patent as a "single bundle of patent rights," albeit patent rights that may have changed with reissuance, for purposes of administering the patent certification requirements of the FD&C Act and any 30-month stay of approval or 180-

day exclusivity that relates to a paragraph IV certification to the original patent (see section V.B.1.e).

We proposed to require that a 505(b)(2) or ANDA applicant provide an appropriate patent certification or statement with respect to a reissued patent, unless the NDA holder did not timely file patent information with FDA on either the original patent or the reissued patent. We also proposed that the patent information listed for the reissued patent would be treated as though it had been submitted under 505(b)(1) or 505(c)(2) of the FD&C Act at the time of listing of the original patent for purposes of determining the availability of a 30-month stay if other criteria were met (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act).

For a first applicant eligible for 180-day exclusivity based on a paragraph IV certification to an original patent that is subsequently reissued, we proposed that if the applicant opined that the reissued patent also is invalid, unenforceable, or will not be infringed, the applicant must submit a paragraph IV certification to the reissued patent within 30 days of the date on which the reissued patent is listed in the Orange Book to lawfully maintain its paragraph IV certification for purposes of eligibility for 180-day exclusivity (see proposed § 314.94(a)(12)(viii)(B)). Otherwise, we proposed that we would consider the first applicant to have amended or withdrawn its paragraph IV certification to the original patent on which it qualified for 180-day exclusivity under section 505(j)(5)(D)(i)(III) of the FD&C Act. We indicated that if a first applicant who qualifies as such based on a paragraph IV certification to the original patent forfeits 180-day exclusivity, another applicant would not be eligible for 180-day exclusivity based on a paragraph IV certification to the reissued patent (see section 505(j)(5)(D)(iii)(II) of the FD&C Act).

In the following paragraphs, we discuss a comment on this proposal (see section V.B.1.e for a discussion of comments regarding submission of additional information on reissued patents). After considering this comment, we are not finalizing this proposal.

(Comment 38) One comment objects to FDA's proposal that a first applicant eligible for 180-day exclusivity based on a paragraph IV certification to a patent that has been reissued must submit a paragraph IV certification to the reissued patent within 30 days of listing to have lawfully maintained its paragraph IV certification for purposes of 180-day exclusivity. The comment asserts that failure to comply with this proposed requirement does not provide an adequate basis for FDA to extinguish a first applicant's eligibility for 180-day exclusivity. In the alternative, the comment requests that FDA expressly state that the requirement only will be applied prospectively. The comment also recommends that an amended patent certification only be required if the original certification becomes inaccurate.

(Response 38) As discussed in Response 17, FDA has determined that the "single bundle of patent rights" approach reflected in its proposed regulations on reissued patents is no longer appropriate based on the recent decision in Mylan Pharms., Inc. v. FDA (594 Fed. Appx. 791). Accordingly, the Agency is not finalizing the proposed revision to § 314.94(a)(12)(viii)(B) regarding reissued patents because we now consider reissued patents as separate and distinct from the original patent for purposes of administering the patent certification requirements of the FD&C Act and any 30-month stay of approval or 180-day exclusivity. This determination that the "single bundle of patent rights" approach is no longer appropriate means that FDA assesses whether a reissued patent is timely filed based solely on whether the NDA holder has submitted the required patent information within 30 days of reissuance (provided that the patent is reissued after the date of approval of the NDA) or otherwise meets the requirements for timely filing of

patent information (see §§ 314.50(i)(4) and 314.94(a)(12)(vi)). Similarly, the date on which patent information on the reissued patent (and not the original patent) is submitted to FDA determines whether a paragraph IV certification to the reissued patent could give rise to a 30-month stay if other criteria are met (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act). This also means that FDA evaluates eligibility for 180-day exclusivity based on whether the criteria are met for an original patent (irrespective of whether it subsequently is reissued) or for a reissued patent. It is unnecessary to address the comment requesting that FDA prospectively apply the proposed revision to § 314.94(a)(12)(viii)(B) because we are not finalizing this proposed change.

With respect to the comment regarding an “amended” patent certification, we note that an appropriate patent certification or statement is required for timely filed patent information submitted by an NDA holder for the listed drug relied upon or RLD, including timely filed patent information on a reissued patent (see §§ 314.50(i)(4) and 314.94(a)(12)(vi), and sections V.B.2.b and V.E.4; see also §§ 314.60(f) and 314.96(d) and section V.F).

#### V.E.4. Other Amended Certifications

We proposed to expressly require a 505(b)(2) or ANDA applicant to submit an appropriate patent certification or statement if, after submission of the 505(b)(2) application or ANDA, a new patent is issued by the USPTO that claims the listed drug or RLD or that claims an approved use for such drug, except as provided in §§ 314.50(i)(4) and 314.94(a)(12)(vi) (see proposed §§ 314.50(i)(6)(iii)(A)(2) and 314.94(a)(12)(viii)(C)(1)(ii)). We also explained our longstanding position that if an applicant that previously submitted a paragraph III certification, a paragraph IV certification, or a statement under section 505(b)(2)(B) or (j)(2)(A)(viii) of the FD&C Act fails to amend its patent certification to a paragraph II certification upon patent

expiration, the Agency will consider the 505(b)(2) or ANDA applicant to have constructively changed its patent certification to a paragraph II certification. We proposed that a patent certification or statement by an ANDA applicant must not be submitted earlier than the first working day after the day the patent is published in the Orange Book (see proposed § 314.94(a)(12)(viii)(C)(1)(ii); see also proposed § 314.95(b)(2) and section V.D.1.a). Finally, we proposed to revise our regulations to clarify that an applicant is not required to submit a supplement solely to change a submitted patent certification after approval of the application (see proposed §§ 314.50(i)(6)(iii)(B) and 314.94(a)(12)(viii)(C)(2)).

In section V.D.1.a, we discuss comments on proposed § 314.94(a)(12)(viii)(C)(1)(ii) (see Responses 33 and 34). We received no other comments and are finalizing these provisions without change, except for the technical amendments described in section V.P.4.

#### V.F. Patent Certification Requirements for Amendments and Supplements to 505(b)(2)

##### Applications and ANDAs (§§ 314.60, 314.70, 314.96, and 314.97)

#### V.F.1. Types of Amendments for Which Patent Certification is Required

We proposed to add §§ 314.60(f) and 314.96(d) to clarify and augment the patent certification requirements for amendments described in §§ 314.50(i)(6)(iii) and 314.94(a)(12)(viii)(C). In these provisions, we proposed to require that an applicant must submit patent certifications described in §§ 314.50(i) or 314.94(a)(12) if approval is sought for any of the following types of amendments to a 505(b)(2) application or ANDA: (1) To add a new indication or other condition of use; (2) to add a new strength; (3) to make other than minor changes in the product formulation; or (4) to change the physical form or crystalline structure of the active ingredient of the drug product.

We explained that this proposed requirement would not apply to minor changes in product formulation that FDA would regard as resulting in essentially the same product (see proposed §§ 314.60(f)(3) and 314.96(d)(3)). We proposed that a new patent certification would not be required if the new formulation in the amendment is qualitatively (Q1) the same as the previous formulation (i.e., contains all of the same inactive ingredients) and quantitatively (Q2) essentially the same (i.e., each inactive ingredient differs by no more than plus or minus 5 percent from the previous formulation). If an applicant submits an amendment to a 505(b)(2) application or ANDA for any of the categories of changes described in these provisions and does not submit a new patent certification, we proposed that the applicant would be required to verify that the proposed change described in the amendment is not the type of change for which a new patent certification or statement is required (e.g., the proposed formulation change meets the criteria for a “minor” formulation change).

In the following paragraphs, we discuss several comments on this proposal. After considering these comments, we are finalizing §§ 314.60(f) and 314.96(d) with revisions to clarify that the specified types of amendments are required to contain an appropriate patent certification (or recertification) or statement and to describe the required verification.

(Comment 39) Three comments recommend that an amended patent certification should not be required if the 505(b)(2) or ANDA applicant determines that the change described in its amendment does not materially affect the factual and legal basis for a previous paragraph IV certification or materially affect the product in a manner that could be protected by a listed patent. These comments express concern that requiring a patent certification for the types of amendments described in §§ 314.60(f) and 314.96(d) could give rise to a second 30-month stay of approval, contrary to the intent of the MMA. Two other comments opine that the proposal is



under-inclusive, and recommend that FDA require a new patent certification in all circumstances in which an amendment may alter the proposed product's relationship to a listed patent and require that the applicant provide the basis for a claim of noninfringement. These comments recommend requiring a new patent certification (and corresponding opportunity for resolution of potential patent infringement claims before approval) if approval is sought for any of the following types of changes: Any change in product formulation; a change in the physical form, particle size, grade, purity, or crystalline structure of the active ingredient; or a change to a proposed drug-delivery device.

(Response 39) We acknowledge comments suggesting that the patent certification requirements for amendments to a 505(b)(2) application or ANDA may be considered either under-inclusive or over-inclusive. However, we believe that our approach strikes an appropriate balance by protecting the patent rights of NDA holders without unnecessarily delaying approval of 505(b)(2) applications and ANDAs. A 505(b)(2) or ANDA applicant is required to amend its patent certification if, at any time before approval, the applicant learns that the previously submitted patent certification is no longer accurate with respect to the pending application or supplement, as amended (see §§ 314.50(i)(6)(iii) and 314.94(a)(12)(viii)(C)). An applicant that submits a 505(b)(2) application or ANDA containing a paragraph IV certification to a listed patent must reevaluate whether the patent certification continues to be accurate after a change to the proposed product submitted in an amendment to the 505(b)(2) application or ANDA. To address concerns that the factual and legal basis of the applicant's opinion that a patent will not be infringed may have changed, we are requiring an applicant to submit an appropriate patent certification (or recertification, for a previously submitted paragraph IV certification) or statement, for the following types of amendments to a 505(b)(2) application or ANDA: (1) To

add a new indication or other condition of use; (2) to add a new strength; (3) to make other than minor changes in the product formulation; or (4) to change the physical form or crystalline structure of the active ingredient of the drug product (see §§ 314.60(f)(1) and 314.96(d)(1) and Response 42). These patent certification requirements are intended to facilitate ongoing compliance with section 505(b)(2)(A) and (j)(2)(A)(vii) of the FD&C Act. We do not agree that the need for an appropriate patent certification (or recertification) or statement for the types of amendments described in §§ 314.60(f) and 314.96(d) should be left entirely to the applicant's discretion because applicants may be uncertain when it is necessary. To implement the proposed verification by the 505(b)(2) or ANDA applicant described in the proposed rule (see 80 FR 6802 at 6823), we are adding §§ 314.60(f)(2) and 314.96(d)(2) to require that if the amendment to the 505(b)(2) application or ANDA does not contain a patent certification or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described in §§ 314.60(f)(1)(i) through (iv) and 314.96(d)(1)(i) through (iv).

We also do not agree that it is necessary to expressly require an appropriate patent certification (or recertification) with the broader range of changes to a proposed product described in the comments. We previously have explained that “[g]iven the range of changes that may be the subject of a [chemistry, manufacturing, and controls] amendment, such a requirement would impose a significant burden without clearly enhancing compliance with the statutory patent certification requirements. Through our proposal to require a new patent certification and, with respect to a paragraph IV certification, a new notice of paragraph IV certification to be sent at the same time that certain types of amendments are submitted to FDA, we are upholding the legislative balance of the Hatch-Waxman Amendments that facilitates the availability of generic drug products while protecting innovator intellectual property rights” (see

Letter from Janet Woodcock, M.D., Director, CDER, to John B. Dubeck and Frederick A. Stearns, dated February 6, 2015, regarding Docket No. FDA-2003-P-0519, available at <http://www.regulations.gov>).

We recognize that a 30-month stay of approval may result from initiation of a patent infringement action in response to a second notice of paragraph IV certification that is provided with an amendment to a 505(b)(2) application or ANDA. This scenario may occur if the patent at issue in the infringement action was listed before the date of submission of the original 505(b)(2) application or ANDA and, for example, the infringement action was warranted by the change proposed in the amendment (see, e.g., Letter from Janet Woodcock, M.D., Director, CDER, to Gerald F. Masoudi, dated October 19, 2010, regarding Docket No. FDA-2010-P-0223, available at <http://www.regulations.gov> (concluding that a new 30-month stay of approval stems from a timely lawsuit based on the second notice of paragraph IV certification submitted in connection with an amendment to the ANDA for reformulated doxercalciferol injection); Letter from Janet Woodcock, M.D., Director, CDER, to Christina M. Markus, dated June 7, 2011, regarding Docket No. FDA-2011-P-0127, available at <http://www.regulations.gov> (confirming that a second 30-month stay of approval stems from a timely lawsuit based on the second notice of paragraph IV certification submitted in connection with an amendment to the ANDA for desflurane liquid)).

(Comment 40) One comment recommends that an amendment to a 505(b)(2) application or ANDA to add a new indication or other condition of use should only require submission of a patent certification to a patent that claims the new use and for which a patent certification previously was not made.

(Response 40) We agree that if an applicant amends its 505(b)(2) application or ANDA only to add a new indication or other condition of use, the applicant need only certify to listed patents that have been identified as claiming an approved use and relate to the change described in the amendment (provided that the 505(b)(2) application or ANDA contained an appropriate patent certification or statement to any other listed patent(s) prior to submission of the amendment). This approach preserves the NDA holder's intellectual property rights without requiring the 505(b)(2) or ANDA applicant to submit a duplicative certification to a listed patent(s) that has not been identified by the NDA holder as claiming a method of use and would not be implicated by the amendment (compare proposed § 314.70(i)(2)). This approach also is consistent with existing patent certification requirements under §§ 314.50(i)(6)(iii) and 314.94(a)(12)(viii)(C). If any other changes described in paragraphs (ii) through (iv) of §§ 314.60(f)(1) or 314.96(d)(1) are proposed in the amendment, the applicant would be required to address all timely filed listed patents for the listed drug relied upon or RLD with an appropriate patent certification (or recertification) or statement.

An ANDA applicant would be expected to submit an amendment to add a new indication or other condition of use if the applicant previously submitted a statement described in section 505(j)(2)(A)(viii) of the FD&C Act and now seeks approval for the use or if the RLD was approved for a new indication or other condition of use after the ANDA was submitted (see section 505(j)(2)(A)(v) of the FD&C Act and § 314.94(a)(8)(iv)). Most requests for approval of a different indication or condition of use by a 505(b)(2) applicant should not be made as an amendment to the 505(b)(2) application (see § 314.60(b)(6) and guidance for industry entitled "Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees" (December 2004) at 4 to 5, available at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>).

Accordingly, we expect that there would be limited circumstances in which this provision would apply to a 505(b)(2) application (e.g., indication changed from prescription status to OTC use).

#### V.F.2. Types of Supplements for Which Patent Certification Is Required

We proposed to add §§ 314.70(i) and 314.97(c), and make conforming revisions to §§ 314.50(i)(6)(iii)(B) and 314.94(a)(12)(viii)(C)(2), to clarify the patent certification requirements for a 505(b)(2) or ANDA supplement. In these provisions, we proposed to require patent certifications described in § 314.50(i) or § 314.94(a)(12), if the applicant requests approval to add a new indication or other condition of use or to add a new strength in a 505(b)(2) or ANDA supplement (see proposed §§ 314.70(i) and 314.97(c)).

For a 505(b)(2) supplement that seeks approval for a new indication or other condition of use, the 505(b)(2) applicant currently is required to submit an appropriate patent certification or statement for each timely filed patent that claims the listed drug(s) relied upon or a method of using such drug(s) for which the applicant is seeking approval (see section 505(b)(2) of the FD&C Act). We proposed to reduce these patent certification requirements by providing that a 505(b)(2) supplement that only seeks approval to add a new indication or other condition of use is required to contain an appropriate patent certification or statement described in § 314.50(i) only for patents that are identified as claiming an approved use (see proposed § 314.70(i)(2)).

We did not propose to require a patent certification with a supplement to change the formulation or to change the physical form or crystalline structure of the active ingredient of a product approved in a 505(b)(2) application or ANDA. We explained that it would not be necessary for FDA to require patent certifications under these circumstances because the NDA holder for a listed drug and any patent owner can monitor postapproval changes in the

formulation or active ingredient of a marketed drug product and address any patent-related concerns without the involvement of FDA.

In the following paragraphs, we discuss two comments on proposed §§ 314.70(i) and 314.97(c). We are continuing to consider these comments, and thus we are not finalizing proposed §§ 314.70(i) and 314.97(c) (or the references to these provisions in proposed §§ 314.50(i)(6)(iii)(B) and 314.94(a)(12)(viii)(C)(2)), respectively, at this time. Accordingly, FDA will maintain its current practice of regulating directly from the statute and general patent certification regulations in requiring an appropriate patent certification or statement with a 505(b)(2) or ANDA supplement.

(Comment 41) Two comments disagree with FDA's proposal to not expressly require a new patent certification with a 505(b)(2) or ANDA supplement in each of the circumstances in which a new patent certification (or recertification) is required for amendments to a 505(b)(2) application or ANDA. One comment maintains that the Agency's approach is inconsistent with the statute, which clearly describes patent certification requirements for 505(b)(2) and ANDA supplements. This comment also expresses concern that a 505(b)(2) or ANDA applicant could circumvent the patent certification requirements by seeking approval of a noninfringing product that the applicant does not intend to market followed by a supplement for a modified form of the active ingredient or a different formulation of the drug product that the applicant intends to market. Both comments contend that monitoring of postapproval changes by an NDA holder or patent owner is not a replacement for notice from the 505(b)(2) or ANDA applicant of a paragraph IV certification and the opportunity to litigate any potential infringement claims prior to approval of the change requested in the supplement.

(Response 41) We are continuing to evaluate these comments, including whether our regulations should expressly require a new patent certification with a broader range of changes submitted in supplemental applications than described in the proposed rule. Accordingly, we are declining to finalize proposed §§ 314.70(i) and 314.97(c) at this time. We will continue to implement the requirement for an appropriate patent certification or statement with a 505(b)(2) or ANDA supplement directly from the statute and our general regulations on patent certifications (see §§ 314.50(i)(6)(iii) and 314.94(a)(12)(viii)(C) (requiring a 505(b)(2) or ANDA applicant to amend its patent certification if, at any time before approval, the applicant learns that the previously submitted patent certification is no longer accurate with respect to the pending application or supplement)).

#### V.F.3. Requirements for Notice of Paragraph IV Certifications and Implications for 180-Day Exclusivity

We proposed that notice to the NDA holder and each patent owner would be required for all paragraph IV certifications, irrespective of whether the 505(b)(2) or ANDA applicant previously provided notice of paragraph IV certification to the same patent or to another patent claiming the listed drug relied upon or RLD (see section 505(b)(3)(B) and (j)(2)(B)(ii) of the FD&C Act and proposed §§ 314.52(d)(1) and 314.95(d)(1)). We proposed that a first applicant that submits an amendment to its pending ANDA or a supplement would be considered to have lawfully maintained a paragraph IV certification to the patent upon which eligibility for 180-day exclusivity was based if the amendment is accompanied by another paragraph IV certification to the patent and notice of paragraph IV certification is sent in accordance with proposed § 314.95(d).

In the following paragraphs, we discuss two comments on this topic. After considering these comments, we are revising proposed § 314.96(d) regarding amendments to an ANDA to clarify that a paragraph IV certification to a patent or patent claim for which an ANDA applicant previously submitted a paragraph IV certification is a “recertification” rather than an “amendment” of the paragraph IV certification. We are making conforming revisions to § 314.60(f). We are finalizing § 314.52(d)(1) with the changes described in Response 32, and we are finalizing § 314.95(d)(1) with the changes described in section V.D.1.b and the technical amendments described in section V.P.1.

(Comment 42) One comment expresses concern that a first applicant could inadvertently forfeit its eligibility for 180-day exclusivity if, pursuant to proposed § 314.96(d), the first applicant submits a new paragraph IV certification to the patent that qualified the applicant for 180-day exclusivity (see section 505(j)(5)(D)(i)(III) of the FD&C Act). The comment suggests that FDA require an ANDA applicant to provide a new notice of its paragraph IV certification to the NDA holder and each patent owner instead of submitting a new patent certification to the Agency. Another comment recommends that FDA not require an ANDA applicant to submit a new patent certification with an amendment to the ANDA if a patent infringement action already has been filed against the applicant with respect to the ANDA.

(Response 42) FDA interprets the statute to mean that a first applicant “lawfully maintains” a paragraph IV certification to the patent or patent claim upon which eligibility for 180-day exclusivity is based if any subsequent amendment to the ANDA that requires a patent certification contains a paragraph IV certification to the qualifying patent or patent claim and notice of the paragraph IV certification is sent in accordance with § 314.95(d). This interpretation is supported by our longstanding requirement that an ANDA applicant must amend



a submitted certification if, at any time before approval of the ANDA, the applicant learns that the submitted certification is no longer accurate (see § 314.94(a)(12)(viii)(C)(1)(i)). A subsequent paragraph IV certification to the qualifying patent or patent claim is not an “amendment” of the previously submitted paragraph IV certification under section 505(j)(5)(D)(i)(III) of the FD&C Act because the type of certification remains the same; rather, it is a reaffirmation of the patent challenge notwithstanding the amendment to the ANDA. Therefore, we are using the term “recertification” to describe this scenario (see § 314.96(d)(1); see also § 314.60(f)(1)).

We decline to adopt the comment’s proposal to require a new notice of paragraph IV certification--but not a new patent certification--with an amendment to the ANDA. Notice of a paragraph IV certification is inextricably linked to the submission of a corresponding paragraph IV certification. The statute expressly requires that an applicant that submits a paragraph IV certification in an amendment to the ANDA provide the required notice at the time of submission of the amendment regardless of whether the applicant has already given notice with respect to another such certification contained in the application (see section 505(j)(2)(B)(ii)(II) of the FD&C Act). Notice of a new paragraph IV certification submitted with an amendment to the ANDA must be updated to correspond to the proposed product as changed by the amendment. However, we believe that the concern described in the comment is addressed by our explanation that a paragraph IV certification to a patent or patent claim for which an ANDA applicant previously submitted a paragraph IV certification is a “recertification” rather than an “amendment” of the paragraph IV certification and by the corresponding changes to § 314.96(d)(1).

We also do not agree with the suggestion that a new notice of paragraph IV certification should not be required if the NDA holder or owner of the relevant patent(s) already is litigating claims of patent infringement against the ANDA applicant. As previously discussed, the statute requires an ANDA applicant to provide notice with all paragraph IV certifications (see section 505(j)(2)(B)(ii)(II) of the FD&C Act). Moreover, if the factual and legal bases for the paragraph IV certification have changed, it would be particularly important to timely provide this information to the NDA holder and each patent owner to support the efficient use of judicial resources.

V.G. Amendments or Supplements to a 505(b)(2) Application for a Different Drug and  
Amendments or Supplements to an ANDA That Reference a Different Listed Drug  
(§§ 314.60, 314.70, 314.96, and 314.97)

V.G.1. Amendments and Supplements to an ANDA (§§ 314.96(c) and 314.97(b))

We proposed to establish a regulation that would implement section 505(j)(2)(D)(i) of the FD&C Act by providing that an ANDA applicant may not amend or supplement an ANDA to seek approval of a drug referring to a listed drug that is different from the RLD identified in the ANDA (see proposed §§ 314.96(c) and 314.97(b)). For example, we proposed that if at any time before approval of the ANDA, an NDA is approved for a drug product that is pharmaceutically equivalent to the proposed product in the pending ANDA and that NDA is designated as an RLD, the applicant would not be permitted to amend its pending ANDA to reference the new RLD (see proposed § 314.96(c)). We proposed that this restriction also would apply if one or more changes proposed in an amendment or a supplement to an ANDA would result in the proposed product being a pharmaceutical equivalent to a different listed drug than the RLD identified in the ANDA. In these scenarios, we proposed that the ANDA applicant would be

required to submit a new ANDA to identify the pharmaceutically equivalent product as the new RLD (see proposed §§ 314.96(c) and 314.97(b) and section 505(j)(2)(D)(i) of the FD&C Act).

In the proposed rule, we confirmed that different strengths of an approved drug product continue to be regarded as different listed drugs. However, to implement section 505(j)(2)(D)(ii) of the FD&C Act, we proposed to codify our practice that permits an applicant to amend or supplement an ANDA to seek approval of a different strength of the drug (see proposed §§ 314.96(c) and 314.97(b)).

We received no comments on proposed § 314.97(b) regarding supplements. In the following paragraphs, we discuss three comments on proposed § 314.96(c) regarding amendments. After considering these comments, we are finalizing proposed §§ 314.96(c) and 314.97(b) without change.

(Comment 43) One comment requests that FDA modify the proposed regulation to require that if, at any time before submission (rather than any time before approval) of the ANDA, an NDA is approved for a drug product that is pharmaceutically equivalent to the proposed product and that NDA is designated as an RLD, the ANDA applicant would be required to submit an ANDA that identifies the pharmaceutically equivalent product as the RLD. The comment suggests that this proposed revision (and a similar proposal discussed in comment 49) would harmonize FDA's proposed requirements for ANDAs and 505(b)(2) applications by imposing limitations up until the time of ANDA submission rather than approval. Another comment expresses concern that requiring an ANDA applicant to submit a new ANDA that identifies the pharmaceutically equivalent product as the RLD may unnecessarily require additional data and delay ANDA approval, although the comment acknowledges that this may be appropriate and efficient in some circumstances.

(Response 43) We decline to adopt the suggested modification to proposed § 314.96(c). Under existing practice, FDA will refuse to receive an ANDA that does not cite an appropriate RLD or rely on an approved suitability petition as its basis for ANDA submission (see § 314.94(a)(3)). In addition, there are circumstances in which an ANDA that has been received, but not approved, may be required to submit a new ANDA that identifies a pharmaceutically equivalent product as the RLD. This may occur, for example: (1) If a pharmaceutically equivalent product is approved after an ANDA is submitted pursuant to an approved suitability petition (petitioned ANDA) or (2) if changes are proposed in an amendment or a supplement to the ANDA such that the proposed product is pharmaceutically equivalent to a different listed drug than the RLD identified in the original ANDA (modified ANDA). Before enactment of the MMA, FDA required an applicant to amend its ANDA in these scenarios to cite the pharmaceutically equivalent product as its RLD. However, the MMA prohibits an ANDA applicant from amending its ANDA to change the RLD (see section 505(j)(2)(D)(i) of the FD&C Act). Accordingly, for the applicant to obtain approval of the proposed product under section 505(j) of the FD&C Act in these scenarios, we require the applicant to submit a new ANDA that identifies the pharmaceutically equivalent product as its RLD and complies with applicable statutory and regulatory requirements.

We require an ANDA applicant to identify as its RLD a pharmaceutically equivalent product approved any time before approval, rather than submission, of the ANDA, because a generic drug product must demonstrate, among other things, that it is bioequivalent to the RLD to obtain approval (see section 505(j)(2)(A)(iv) of the FD&C Act and § 314.127(a)(6)(i)). We disagree that an ANDA applicant should only be required to identify a pharmaceutically equivalent product as its RLD until submission of the ANDA, because this approach would not

ensure that an ANDA applicant cites an appropriate RLD in the context of a petitioned ANDA or modified ANDA unless the RLD was approved before submission of the ANDA. Such an approach would foster a potentially confusing proliferation of pharmaceutically equivalent drug products that have not demonstrated therapeutic equivalence to the RLD. The additional data and time that may be needed for an ANDA applicant to identify a pharmaceutically equivalent drug product as the RLD is warranted by the need for a clear determination of therapeutic equivalence. The modification requested in the comment would “diminish the utility and accuracy of FDA’s therapeutic equivalence determinations and potentially allow ANDA applicants to circumvent otherwise applicable patent and exclusivity rights accorded the NDA holder for the pharmaceutically equivalent RLD” (see Letter from Janet Woodcock, M.D., Director, CDER, to Mark S. Aikman, Pharm.D., Osmotica Pharmaceutical Corp., dated November 25, 2008, regarding Docket No. FDA-2008-P-0329, at 11-12, available at <http://www.regulations.gov>) (Venlafaxine ER CP Response).

Unlike an ANDA that relies on a single RLD, a 505(b)(2) application may rely for approval on one or more listed drugs and is not required to demonstrate bioequivalence or pharmaceutical equivalence to a listed drug on which it relies for approval. Although the Agency requires a 505(b)(2) applicant to rely upon a drug product approved in an NDA that is pharmaceutically equivalent to the proposed product, the basis and timeframe for this requirement for 505(b)(2) applications differs from that of ANDAs.

(Comment 44) One comment recommends that FDA permit an ANDA applicant to amend its ANDA if FDA changes the RLD or the ANDA applicant petitions to change the RLD.

(Response 44) The comment is unclear because the Agency’s designation of an additional RLD or selection of a new reference standard generally would not require an ANDA

applicant to change its RLD. The RLD is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA (see § 314.3(b)). An ANDA applicant is prohibited from amending or supplementing its ANDA to change the RLD after the ANDA has been submitted (see §§ 314.96(c) and 314.97(b) and section 505(j)(2)(D)(i) of the FD&C Act).

We note that if there are two or more approved NDAs for pharmaceutically equivalent products, a person may submit a citizen petition requesting that FDA designate an additional RLD, provided that there is adequate justification (see “Abbreviated New Drug Application Regulations; Final Rule,” 57 FR 17950 at 17958, April 28, 1992, and section 1.4 of the preface to the Orange Book (36th Edition, 2016, at ix) (recognizing that a listed drug that is not designated as the RLD may be shielded from generic competition)). An ANDA would not be ineligible for approval because it relied on one of two or more RLDs that were approved under section 505(c) of the FD&C Act based on full reports of investigations of safety and effectiveness, provided that other statutory and regulatory requirements are met. Thus, an applicant is not required to change its RLD upon FDA designation of the additional RLD.

Generally, the RLD also will be the reference standard, which is the drug product selected by FDA that an ANDA applicant must use in conducting an in vivo bioequivalence study required for ANDA approval (see §§ 314.3(b) and 314.94(a)(3)). FDA usually selects as the reference standard the highest strength available for drug products with multiple approved strengths. However, a person may petition the Agency to request that FDA designate a new reference standard for conducting bioequivalence testing if, for example, the person believes that another drug product would be a scientifically appropriate reference standard, or if the drug product selected as the reference standard has been discontinued and FDA has not selected a new

reference standard. FDA also may select a reference standard in the absence of a citizen petition (see Letter from Janet Woodcock, M.D., Director, CDER, to Paul A. Braier, Ph.D., J.D., dated September 5, 2014, regarding Docket No. FDA-2014-P-0417, at 11, available at <http://www.regulations.gov>). For example, if the RLD has been withdrawn from marketing for reasons other than safety or effectiveness, FDA may select a different drug product (e.g., a different strength of a drug product that is the RLD) or a therapeutically equivalent drug product (e.g., an approved ANDA that cited the RLD as its basis of submission) as the reference standard. Even if FDA selects a reference standard that is a drug product other than the RLD for use in conducting an in vivo bioequivalence study, the proposed drug product will be evaluated against the RLD to determine whether it meets the statutory requirements for approval under section 505(j) of the FD&C Act. An applicant also may request, with appropriate scientific justification, that FDA waive the requirement to use the drug selected by FDA as the reference standard in an in vivo bioequivalence study required for approval (see § 314.99(b)).

FDA's selection of a different reference standard or waiver of the requirement to use the reference standard generally would not result in a change to the RLD. An ANDA would not be ineligible for approval because it relied upon an RLD that was not selected as a reference standard.

We acknowledge that FDA's practice of identifying the reference standard in the Orange Book by the word "yes" in the "RLD" column has resulted in confusion, and we are revising the column heading in the Orange Book from "RLD" to "RS" for clarity.

#### V.G.2. Amendments and Supplements to a 505(b)(2) Application (§§ 314.60(e) and 314.70(h))

We proposed to establish a regulation that would implement section 505(b)(4)(A) of the FD&C Act by providing that an applicant may not amend or supplement a 505(b)(2) application

to seek approval of a drug that is a different drug from the drug in the original submission of the 505(b)(2) application (see proposed §§ 314.60(e) and 314.70(h)). We proposed that a drug will be considered a “different drug” for purposes of section 505(b)(4)(A) of the FD&C Act if it has been modified to have a different active ingredient, different route of administration, different dosage form, or different excipients that require either a separate clinical study to establish safety or effectiveness or, for topical products, that require a separate in vivo demonstration of bioequivalence (see proposed §§ 314.60(e) and 314.70(h)). These proposed modifications would result in a different drug for which approval must be requested in a new 505(b)(2) application.

In the proposed rule, we explained that the statutory restriction on amending a 505(b)(2) application to seek approval of a drug that is a different drug from the drug in the original submission of the 505(b)(2) application applies to any proposed amendment, even if the amendment is submitted before the Agency’s decision regarding whether the 505(b)(2) application can be filed in accordance with § 314.101(a). However, notwithstanding these restrictions on amendments to a 505(b)(2) application, we proposed that an applicant is permitted to amend or supplement a 505(b)(2) application to identify a new or additional listed drug upon which the application relies for approval as long as the applicant is not seeking approval for a different drug from the drug in the original submission of the 505(b)(2) application. In addition, we proposed that an applicant is permitted to amend or supplement a 505(b)(2) application to seek approval for a different strength of the drug product (see section 505(b)(4)(B) of the FD&C Act and proposed §§ 314.60(e) and 314.70(h)).

We received no comments on proposed § 314.70(h) regarding supplements. In the following paragraphs, we discuss a comment on proposed § 314.60(e) regarding amendments.



After considering this comment, we are finalizing proposed §§ 314.60(e) and 314.70(h) without change.

(Comment 45) One comment recommends that FDA return to its initial interpretation of section 505(b)(4)(A) of the FD&C Act and revise § 314.60(e) to prohibit a 505(b)(2) applicant from amending its application to rely upon a new or different listed drug for approval. The comment observes that if a new or different listed drug is identified in an amendment to the 505(b)(2) application, and the 505(b)(2) applicant submits a paragraph IV certification for a patent that is timely filed after submission of the 505(b)(2) application, a 30-month stay would not be available should the NDA holder or patent owner initiate patent infringement litigation within the statutory timeframe.

(Response 45) We decline to revise § 314.60(e) as requested because the comment does not provide any basis for a different interpretation of section 505(b)(4)(A) of the FD&C Act that FDA did not expressly consider in the proposed rule. The preamble to the proposed rule contains an extensive discussion of the Agency's initial interpretation of section 505(b)(4)(A) of the FD&C Act and explains why FDA proposed narrowing that interpretation of section 505(b)(4)(A) of the FD&C Act as reflected in §§ 314.60(e) and 314.70(h) (see 80 FR 6802 at 6850 through 6852). The comment has not persuaded us to return to that initial interpretation.

V.H. Procedure for Submission of a 505(b)(2) Application Requiring Investigations for Approval of a New Indication for, or Other Change From, a Listed Drug (§ 314.54)

We proposed to require that the listed drug(s) identified as relied upon by a 505(b)(2) applicant must include any approved drug product that: (1) Is pharmaceutically equivalent to the drug product for which the 505(b)(2) application is submitted and (2) was approved before the

505(b)(2) application was submitted (see proposed §§ 314.50(i)(1)(i)(C), 314.54(a)(1), and 314.125(b)(19)).

In the following paragraphs, we discuss a comment on these proposed provisions. After considering this comment, we are finalizing proposed § 314.54(a)(1) with revisions to clarify that a 505(b)(2) applicant must identify a pharmaceutically equivalent drug product approved in an NDA as a listed drug (or an additional listed drug) relied upon if the pharmaceutically equivalent drug product was approved before the date of submission of the original 505(b)(2) application, and to codify the basis for this requirement. If there is more than one drug product that is pharmaceutically equivalent to the drug product for which the original 505(b)(2) application is submitted and was approved in one or more NDAs before the original 505(b)(2) application was submitted, the 505(b)(2) applicant is only required to identify one such pharmaceutically equivalent drug product as a listed drug relied upon. We are finalizing proposed §§ 314.50(i)(1)(i)(C) and 314.125(b)(19) with conforming revisions.

(Comment 46) One comment suggests that FDA require a 505(b)(2) applicant to identify any approved pharmaceutically equivalent drug product as a listed drug relied upon to support approval of the proposed product irrespective of whether the pharmaceutically equivalent product was approved before or during the review of the 505(b)(2) application. The comment proposes that if a pharmaceutically equivalent product is approved after a 505(b)(2) application is submitted, the 505(b)(2) applicant--like an ANDA applicant--should be required to file a new 505(b)(2) application to ensure that the NDA holder for the pharmaceutically equivalent drug product has a reasonable opportunity for a 30-month stay and that any non-patent exclusivity is meaningful.

(Response 46) We decline to modify the regulations as suggested. If a pharmaceutically equivalent drug product is approved before an original 505(b)(2) application is submitted, we consider the 505(b)(2) applicant to implicitly rely upon FDA's finding of safety and effectiveness for one such pharmaceutically equivalent drug product for approval even if the proposed drug product was developed independently of that pharmaceutically equivalent drug product. Accordingly, we require the 505(b)(2) applicant to identify one pharmaceutically equivalent drug product approved in an NDA as a listed drug (or an additional listed drug) relied upon and comply with applicable regulatory requirements. A 505(b)(2) applicant that identifies a listed drug solely to comply with § 314.54(a)(1)(vi) must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent drug product, but the 505(b)(2) applicant is not required to submit bridging data to justify the scientific appropriateness of reliance on the pharmaceutically equivalent drug product if it is scientifically unnecessary to support approval. Given that there cannot be any implicit reliance on FDA's finding of safety and effectiveness for a drug product that has not yet been approved, this rationale would not support a requirement for a 505(b)(2) applicant to identify a pharmaceutically equivalent drug product approved in an NDA after the 505(b)(2) application is submitted. We are revising § 314.54(a)(1)(vi) to clarify the basis for this requirement, which establishes a bright line requirement for administering the patent certification requirements of the FD&C Act and is unrelated to our approach to implementing section 505(b)(4)(A) of the FD&C Act. We are further revising the regulations to clarify that the requirement to identify one pharmaceutically equivalent drug product approved in an NDA as a listed drug (or an additional listed drug) relied upon applies before the date of submission of an original 505(b)(2) application and not a resubmission or a supplement (see, e.g., § 314.54(a)(1);

see also § 314.3(b) (definitions of “original NDA” and “resubmission”). We also are making conforming revisions to § 314.54(a)(1)(iii) and (vi) to clarify that a 505(b)(2) application may rely on FDA’s finding of safety and/or effectiveness for one or more listed drugs.

We recognize that a 505(b)(2) applicant that does not amend its pending 505(b)(2) application to rely upon a pharmaceutically equivalent listed drug would have no occasion to submit a patent certification or statement with respect to any patents listed for the listed drug (and could be subject to patent infringement litigation after approval). This illustrates one of many circumstances in which the timing of submission of an application has certain statutory or regulatory implications (see, e.g., untimely filing of patent information). However, to the extent that the 505(b)(2) application is seeking approval for the exclusivity-protected conditions of approval for the listed drug, approval of the 505(b)(2) application would be delayed by any applicable 3-year exclusivity for the listed drug irrespective of reliance (see Veloxis Pharms. v. FDA, 109 F. Supp. 3d 104, 120 (D.D.C. 2015)).

(Comment 47) One comment suggests that FDA require a 505(b)(2) applicant to identify any approved drug product that is a pharmaceutical alternative to the proposed product as a listed drug(s) relied upon to support approval of the proposed product.

(Response 47) We decline to modify the regulations as suggested. Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester (see § 314.3(b)). Accordingly, there may be numerous pharmaceutical alternatives to a particular drug product. Given that a proposed drug product intended for submission in a 505(b)(2) application may differ in various respects from the listed drug(s) on which it relies for approval, there is insufficient justification to require a 505(b)(2) applicant to identify any pharmaceutical alternative (in

addition to one pharmaceutical equivalent) as a listed drug upon which the 505(b)(2) application relies in the absence of explicit reliance (see Letter from Janet Woodcock, M.D., Director, CDER, to David B. Clissold, J.D., dated September 18, 2013, regarding Docket Nos. FDA-2011-P-0869 and FDA-2013-P-0995, at 8, available at <http://www.regulations.gov>) (“except where a pharmaceutical equivalent already has been approved, the 505(b)(2) applicant should determine which listed drug(s) is most appropriate for its development program”).

We consider the 505(b)(2) applicant to implicitly rely for approval upon FDA’s finding of safety and effectiveness for one such pharmaceutically equivalent listed drug approved in an NDA because the proposed product shares key characteristics (active ingredient, dosage form, route of administration, and strength) in common with the listed drug despite being ineligible for approval under section 505(j) of the FD&C Act (see § 314.101(d)(9)). As we explained in the proposed rule, the requirement to identify a pharmaceutically equivalent product approved in an NDA as a listed drug upon which the 505(b)(2) application relies “is intended to help ensure that the 505(b)(2) pathway is not used to circumvent the statutory obligation that would have applied if the proposed product was submitted as an ANDA--namely, submission of a patent certification for a listed patent that corresponds to the protected aspects of the pharmaceutically equivalent listed drug” (80 FR 6802 at 6856).

(Comment 48) One comment recommends that FDA clarify that the requirement for a 505(b)(2) applicant to identify an approved pharmaceutically equivalent product as a listed drug relied upon does not extend to a complex drug product for which there may be uncertainty about whether the drug contains the “identical” or “same” active drug ingredient.

(Response 48) We acknowledge that a 505(b)(2) applicant may be uncertain whether to identify a listed drug solely to comply with §§ 314.50(i)(1)(i)(C), 314.54(a)(1), and

314.125(b)(19) due to the applicant's uncertainty about whether the drug contains the "identical" active drug ingredient or meets other criteria for a pharmaceutical equivalent. FDA intends to consider on a case-by-case basis any assertions by a prospective 505(b)(2) applicant that there is uncertainty about whether a previously approved drug product contains the "identical" active drug ingredient as the proposed product.

V.I. Petition to Request a Change From a Listed Drug (§ 314.93)

We proposed to codify FDA's policy that the listed drug identified in an approved suitability petition can no longer be the basis for submission for an unapproved ANDA after a drug product is approved in an NDA for the change described in the petition, irrespective of whether FDA has withdrawn approval of the suitability petition (see proposed § 314.93(f)). We proposed that an applicant may not amend its ANDA to change the basis for submission to the new RLD (see section 505(j)(2)(D)(i) of the FD&C Act and proposed § 314.96(c)), and would be required to submit a new ANDA that relies on the pharmaceutically equivalent RLD if the applicant seeks approval for the drug product. Accordingly, we proposed to add § 314.127(a)(14) to state that FDA will refuse to approve a petitioned ANDA if an NDA subsequently has been approved for the change described in the suitability petition. We also proposed to add § 314.93(e)(1)(vi) to codify our longstanding policy that FDA will not approve a suitability petition if a drug product is approved in an NDA for the change requested in the petition.

One comment agreed with these proposed revisions to our regulations on suitability petitions. In the following paragraph, we discuss two other comments on the proposal. After considering these comments, we are finalizing proposed § 314.93(e) and (f) with the technical amendment described in section V.P.1. We are also finalizing proposed § 314.127(a)(14) with

technical amendments to describe an approved “suitability petition” as an approved petition under 21 CFR 10.30 and § 314.93, and we are making conforming revisions to § 314.94(a)(3)(i) and (iii).

(Comment 49) Two comments recommend that FDA revise the proposed regulation to require that if, at any time before submission (rather than any time before approval) of an ANDA based on a suitability petition, an NDA is approved for the change described in the suitability petition, the ANDA applicant would be required to submit an ANDA that identifies the drug product approved in the NDA as the RLD. One comment suggests that this proposed revision would harmonize FDA’s proposed requirements for ANDAs and 505(b)(2) applications with respect to the timeframe in which an applicant must rely upon a pharmaceutically equivalent product. The other comment observes that there still may be multiple versions of a drug product because one or more ANDAs may have been approved pursuant to the suitability petition before an NDA is approved for the change described in the petition.

(Response 49) We decline to adopt the suggested modification to §§ 314.93 and 314.127(a)(14). FDA’s longstanding practice, as described in the letter granting a suitability petition, is that once a drug product is approved in an NDA for the change described in the petition, that drug product will be the RLD and thereafter the approved suitability petition may not be used as the basis for submission of an ANDA. Accordingly, if an NDA is approved for the change described in the suitability petition before submission of an ANDA pursuant to an approved suitability petition, FDA would refuse to receive the ANDA. If an NDA is approved for the change described in the suitability petition after submission or receipt of an ANDA and is designated as the RLD, the applicant would be required to submit a new ANDA that cites the RLD as its basis for submission, and complies with applicable statutory and regulatory

requirements for approval. As we explained in the proposed rule, our requirement that an applicant with a pending ANDA subject to an approved suitability petition change the RLD upon FDA approval of an NDA for the same drug product described in the approved suitability petition “reflects the Agency’s judgment that considerations regarding an ANDA’s limited reliance on an approved suitability petition are outweighed by the need for a clear determination of therapeutic equivalence for a generic drug product and protection of intellectual property rights accorded an NDA holder” (80 FR 6802 at 6853, quoting Venlafaxine ER CP Response at 9).

#### V.J. Filing an NDA and Receiving an ANDA (§ 314.101)

##### V.J.1. Notification of Filing of a 505(b)(2) Application or Receipt of an ANDA

We proposed to clarify that FDA will notify the applicant that the 505(b)(2) application is regarded as filed or the ANDA is regarded as received by means of a paragraph IV acknowledgment letter if the 505(b)(2) application or ANDA contains a paragraph IV certification (see proposed § 314.101(a)(2) and (b)(2); see also sections V.A.1 and V.D.1.a). We received no comments regarding these proposed revisions, and we are finalizing proposed § 314.101(a)(2) without change, and § 314.101(b)(2) with the clarifying revisions discussed in section V.J.2.

##### V.J.2. Refuse-to-Receive Decisions for ANDAs

We proposed to revise § 314.101(b)(1) and (2) regarding ANDAs to incorporate the statutory definition of a “substantially complete application,” which was added by the MMA for purposes of section 505(j)(5) of the FD&C Act (see section 505(j)(5)(B)(iv)(II)(cc) of the FD&C Act and section V.A.5). We proposed that receipt of an ANDA means that FDA has made a threshold determination that the ANDA is substantially complete (see proposed § 314.101(b)(1)).



We proposed to revise § 314.101(b)(2) to clarify that if an ANDA is determined to have been substantially complete as of the date on which it was submitted, the date of submission is considered to be the date of receipt. We also proposed to amend § 314.101(b)(3) to update the regulations to reflect our current practice for advising an ANDA applicant that FDA has refused to receive the ANDA under § 314.101(d) or (e).

In the following paragraphs, we discuss three comments on these proposed revisions. After considering these comments, we are making clarifying revisions to proposed § 314.101(b)(2). We are finalizing proposed § 314.101(b)(3) and (d)(3) with revisions to more precisely describe the factors that FDA considers in determining whether an ANDA is incomplete on its face, and the actions that an ANDA applicant may take following a refuse-to-receive decision.

(Comment 50) Two comments recommend that FDA clarify its regulations regarding refuse-to-receive standards in light of the policy described in its guidance for industry entitled “ANDA Submissions--Refuse-to-Receive Standards” (May 2015), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. One of these comments maintains that the current regulation permits applicants to amend an ANDA to address deficiencies irrespective of the number of deficiencies or whether the deficiencies are major or minor. This comment asserts that FDA would need to reissue the proposed rule to incorporate the standards described in the guidance. Another comment suggests that FDA limit the time for a completeness evaluation to 90 days, and permit applicants to amend an ANDA to address minor deficiencies that can be corrected within 30 days.

(Response 50) FDA agrees with the recommendations to clarify its regulations regarding refuse-to-receive standards for ANDAs. To address these comments, FDA is revising

§ 314.101(d)(3) to codify its current practice of considering the nature (e.g., major or minor) of the deficiencies, including the number of deficiencies in the ANDA, in determining whether an ANDA is incomplete on its face. This approach reflects the goal of FDA's filing regulations, which encourage applicants to submit complete ANDAs and conserve FDA resources by permitting FDA reviewers to devote their time to examining reviewable applications (57 FR 17950 at 17965).

To clarify the actions that an ANDA applicant may take following a refuse-to-receive decision, FDA is revising § 314.101(b)(3)(ii) to state that if the ANDA is not received, the applicant may correct the deficiencies and resubmit the ANDA. This amendment reflects the statutory procedures for ANDAs that FDA considers not to have been received (see section 744B(a)(3)(E) of the FD&C Act (21 U.S.C. 379j-42(a)(3)(E) (describing the user fee requirements for resubmission of an ANDA that FDA considers not to have been received or that has been withdrawn)). FDA also is revising § 314.101(b)(3)(iii) to clarify that if the ANDA is not received, the applicant may take no action, in which case FDA may consider the ANDA withdrawn after 1 year. An ANDA applicant's failure to take action after a refuse-to-receive decision on an ANDA may be considered a request by the applicant to withdraw the ANDA, unless the applicant requests an extension of time in which to resubmit the ANDA. This revision eliminates the circularity of the former text, which provided that if the ANDA is refused for receipt and the applicant takes no action, FDA will refuse to receive the ANDA.

Finally, FDA is revising § 314.101(b)(2) to clarify that if FDA determines, upon evaluation, that an ANDA was substantially complete as of the date it was submitted to FDA, FDA will consider the ANDA to have been received as of the date of submission. We are making a conforming revision to § 314.101(b)(1) to change "reviewed" to "evaluated" to clarify

that FDA's evaluation does not involve a substantive review of the data in the ANDA. We disagree with the comment's suggestion that reissuance of the proposed rule is necessary for these clarifying revisions to § 314.101 because the revisions are not changing the standard for refuse-to-receive decisions, but are merely clarifying how FDA has been implementing the standard.

(Comment 51) One comment recommends that FDA provide a mechanism for ANDA applicants to challenge a refuse-to-receive decision analogous to the procedures described in § 314.101(a)(3) for NDA applicants.

(Response 51) FDA declines to adopt the suggestion because a revision to the regulations is not necessary to provide a mechanism for ANDA applicants to dispute a refuse-to-receive decision. ANDA applicants can avail themselves of existing mechanisms to discuss or dispute a refuse-to-receive action, including the dispute resolution procedure in § 314.103.

#### V.J.3. Administrative Consequence for Late Notice

We proposed to establish an administrative consequence for an ANDA applicant that fails to timely provide notice of a paragraph IV certification (see section 505(j)(2)(B)(ii) of the FD&C Act). We proposed that if FDA determines that an ANDA applicant did not send notice of a paragraph IV certification within the timeframe described in § 314.95(b) or (d), as applicable, FDA will deem the date that the ANDA was submitted to be delayed by the number of days by which the timeframe for sending notice of a paragraph IV certification was exceeded (see proposed § 314.101(b)(4)). This proposal created the potential for an ANDA applicant to lose its first-applicant status and thus its eligibility for 180-day exclusivity as a result of providing late notice, if another applicant were to submit a substantially complete ANDA containing a paragraph IV certification on the same first day and were to provide timely notice (see section

505(j)(5)(B)(iv) of the FD&C Act). We noted that this proposed administrative consequence would not reduce the 30-month timeframe set forth in section 505(j)(5)(D)(i)(I)(aa)(BB) and (j)(5)(D)(i)(IV) of the FD&C Act in the forfeiture calculus for a first applicant; rather, the 30-month period would begin on the revised date of submission.

Two comments support FDA's proposed administrative consequence for failure to send notice of paragraph IV certification within the required timeframe. In the following paragraphs, we discuss two other comments on this proposal. After considering these comments, we are not finalizing proposed § 314.101(b)(4).

(Comment 52) One comment asserts that the statutory consequence for an ANDA applicant's delay in sending notice of paragraph IV certification is a commensurate delay in the start of any resultant 30-month stay of approval. The comment contends that the Agency has no legal authority to impose an additional sanction, and that the proposal should be withdrawn. Another comment recommends that the administrative consequence for a first applicant be modified to reduce the 180-day exclusivity period by the number of days that notice was late and avoid the potential loss of eligibility for 180-day exclusivity.

(Response 52) Although we believe that the Agency has the authority to establish an administrative consequence for an ANDA applicant's failure to comply with the statutory timeframe for sending notice of paragraph IV certification, we currently do not consider the administrative consequence to be necessary in light of other incentives for ANDA applicants to timely provide notice of a paragraph IV certification. Based on the Agency's implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA) in Title III of FDASIA and the GDUFA goals for expeditious review of ANDAs, FDA is approving ANDAs more quickly and ANDA applicants are unlikely to delay sending notice of paragraph IV certification because such

a delay might result in a delay in ANDA approval. A 505(b)(2) or ANDA applicant that provides late notice of a paragraph IV certification risks that the NDA holder or patent owner will file an action for patent infringement within the 45-day period after notice, and that any resultant 30-month stay will delay approval by a period of time commensurate with the 505(b)(2) or ANDA applicant's delay in sending notice. We believe this potential delay in approval will incentivize 505(b)(2) and ANDA applicants to comply with the statutory timeframe for sending notice, and provide adequate opportunity for an NDA holder or patent owner to assert certain intellectual property rights prior to approval. Accordingly, we are declining to finalize the proposed administrative consequence as unnecessary at this time.

#### V.J.4. Other Proposed Revisions

We proposed several clarifying revisions to § 314.101. First, we proposed to delete the reference to section 507 of the FD&C Act in § 314.101(d)(3) to reflect statutory changes made by the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115). Second, we proposed to replace the term “application” in § 314.101(d)(6) and (7) with “NDA or ANDA” to clarify that these provisions apply to ANDAs as well as NDAs. Third, we proposed to replace the current text of § 314.101(e)(2) with a statement that FDA will refuse to file a 505(b)(2) application or will consider an ANDA not to have been received if submission of a 505(b)(2) application or an ANDA is not permitted under § 314.108(b)(2).

We received no comments regarding these proposed revisions, and we are finalizing these revisions to § 314.101(d)(3), (6), and (7) without change. We are making conforming revisions to § 314.101(d)(5) and the paragraph heading for § 314.101(d). As discussed in section V.A.7, we are revising § 314.101(e)(2) to remove the cross-reference to § 314.108(b)(2) because that section does not address all of the potential exclusivities that would preclude a 505(b)(2)

application or ANDA from being filed or received. We are also revising § 314.101(e)(2) to expressly state that FDA will refuse to file an NDA or will consider an ANDA not to have been received if submission of a 505(b)(2) application or an ANDA is not permitted under section 505(c)(3)(E)(ii), 505(j)(5)(F)(ii), 505A(b)(1)(A)(i)(I), 505A(c)(1)(A)(i)(I), or 505E(a) of the FD&C Act.

V.K. Approval of an NDA and ANDA (§ 314.105)

We proposed to revise § 314.105(a) and (d) regarding approval of an NDA and an ANDA to remove the references to a “delayed effective date” and clarify that an application is approved on the date of issuance of an approval letter. We explained in the proposed rule that the Agency does not issue approval letters with delayed effective dates. Rather, the Agency will issue a tentative approval letter when an NDA or ANDA that is otherwise eligible for approval cannot be approved because of unexpired patents, certain circumstances related to patent litigation, or various types of exclusivity.

In addition, we proposed to revise § 314.105(a) and (d) to expressly state that FDA’s tentative approval of a drug product is based on information available to FDA at the time of the tentative approval letter (i.e., information in the 505(b)(2) application or ANDA and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to FDA’s attention.

We received no comments regarding these proposed revisions. We are finalizing § 314.105 without change, except for the technical amendments described in section V.A.3 and V.A.7 to reflect the enactment of GAIN and IRTNMTA, respectively.

V.L. Refusal to Approve an NDA or ANDA (§§ 314.125 and 314.127 and Related Provisions in §§ 314.90 and 314.99)

We proposed to revise §§ 314.90 and 314.99 to clarify that if FDA grants an applicant's request for waiver of a requirement under §§ 314.50 through 314.81 or §§ 314.92 through 314.99, respectively, the applicant's failure to comply with the requirement that is the subject of the waiver request will not constitute a basis for refusal to approve the NDA under § 314.125 or the ANDA under § 314.127. We also proposed corresponding revisions to §§ 314.125(b) and 314.127(a), which address permissive refusal to approve an NDA and mandatory refusal to approve an ANDA, respectively. We received no comments regarding these proposed revisions, and we are finalizing these provisions without change.

V.M. Date of Approval of a 505(b)(2) Application or ANDA (§ 314.107)

V.M.1. General (§ 314.107(a))

We proposed to revise the general regulation that describes the “effective date of approval” of a 505(b)(2) application or ANDA and the date on which the approval of a 505(b)(2) application or ANDA “becomes effective” to simply refer to the date the 505(b)(2) application or ANDA “is approved” (see proposed § 314.107(a)). In the proposed rule, we explained that FDA does not issue approval letters with delayed effective dates. We received no comments on these revisions, and we are finalizing proposed § 314.107(a) without change.

V.M.2. Effect of Patent(s) on the Listed Drug (§ 314.107(b))

We proposed to revise the regulation that describes the effect of one or more patents on the listed drug(s) relied upon or the RLD on the timing of approval of a 505(b)(2) application or ANDA, respectively (see proposed § 314.107(b)). We proposed to clarify that an analysis is required for each relevant patent to determine the first possible date on which the 505(b)(2)

application or ANDA can be approved based on the patent certification(s) and/or statement(s) submitted by the applicant (see proposed § 314.107(b)). We proposed that the 505(b)(2) application or ANDA may be eligible for approval on the last applicable date for all relevant patents listed in the Orange Book (see proposed § 314.107(b) and proposed deletion of § 314.107(b)(4)). In the proposed rule, we explained that an analysis of the effect of one or more patents on the timing of approval of a 505(b)(2) application or ANDA is made when the 505(b)(2) application or ANDA is otherwise eligible for approval. We received no comments on these revisions, and we are finalizing the introductory text of proposed § 314.107(b) with the IRTNTMA-related revisions described in section V.A.3.

V.M.2.a. Timing of approval based on patent certification or statement (§ 314.107(b)(1)). We proposed to describe the timing of approval of a 505(b)(2) application or ANDA based on the patent certification(s) and/or statement(s) submitted by the applicant for each relevant patent (see proposed § 314.107(b)(1)). We proposed to reorganize the regulation and describe the types of patent certifications or statements that would result in an immediate first possible date on which a 505(b)(2) application or ANDA may be approved (see proposed § 314.107(b)(1)(i) and (ii)) or in a delay in the first possible approval date until the date on which a patent will expire (see proposed § 314.107(b)(1)(iii)).

We proposed to clarify that, except as provided in § 314.107(b)(3) and (c), a 505(b)(2) application or ANDA containing a paragraph IV certification may be eligible for immediate approval only if the 45-day period provided for in section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act has expired (see proposed § 314.107(b)(1)(i)(C)). We also proposed to clarify that if a 505(b)(2) or ANDA applicant submits a statement under § 314.50(i)(1)(iii) or § 314.94(a)(12)(iii), respectively, explaining that a method-of-use patent does not claim an



indication or other condition of use for which the applicant is seeking approval and submits proposed labeling that appropriately carves out information related to the patented method of use, then the 505(b)(2) application or ANDA may be eligible for immediate approval (see proposed § 314.107(b)(1)(ii)). In the proposed rule, we explained that a listed patent may claim the drug substance and/or drug product in addition to one or more methods of use, and if the 505(b)(2) or ANDA applicant submitted a statement with respect to one or more methods of use and a paragraph IV certification with respect to the remaining claims, the first possible date on which the 505(b)(2) application or ANDA can be approved would be analyzed in accordance with proposed § 314.107(b)(1)(i)(C) and (b)(1)(ii).

We received no comments on proposed § 314.107(b)(1). However, we are revising § 314.107(b)(1)(ii) to expressly state that if a 505(b)(2) or ANDA applicant submits a paragraph IV certification for certain patent claims in addition to a statement under § 314.50(i)(1)(iii) or § 314.94(a)(12)(iii) for other patent claims, a determination of the first possible date on which the 505(b)(2) application or ANDA can be approved also would require an analysis under § 314.107(b)(1)(i)(C). We also are making a minor editorial revision to proposed § 314.107(b)(1) to clarify that the provision applies to a 505(b)(2) application or an ANDA.

V.M.2.b. Patent information filed after submission of 505(b)(2) application or ANDA (§ 314.107(b)(2)). We proposed to clarify the effect of patent information filed after submission of a 505(b)(2) application or ANDA on the timing of approval of the 505(b)(2) application or ANDA (see proposed § 314.107(b)(2)). We proposed that if an NDA holder submits patent information for a listed drug after the date on which a 505(b)(2) application or ANDA relying upon such drug was submitted to FDA, the 505(b)(2) or ANDA applicant must comply with the requirements of §§ 314.50(i)(4) and (i)(6) and 314.94(a)(12)(vi) and (a)(12)(viii) regarding

amendment of its patent certification or statement. We also proposed that if the 505(b)(2) or ANDA applicant submits an amendment containing a paragraph IV certification to a newly listed patent, the 505(b)(2) application or ANDA may be approved immediately upon the submission of an amendment containing documentation that the NDA holder and each patent owner have received notice of the paragraph IV certification, if the 505(b)(2) application or ANDA is otherwise eligible for approval (see proposed § 314.107(b)(2)). We proposed that there is no need to delay approval until the expiration of the 45-day period described in section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act because a 30-month stay of approval is not available in these circumstances.

We received no comments on these revisions. However, we are revising § 314.107(b)(2) to clarify that a 505(b)(2) or ANDA applicant must comply with the regulatory requirements regarding “submission of an appropriate patent certification or statement” to a newly listed patent rather than an “amendment of its patent certification or statement” because the latter phrase may incorrectly suggest a change to an existing patent certification or statement, which would not exist in the case of a newly listed patent. We are making conforming revisions to §§ 314.50(i)(4) and 314.94(a)(12)(vi).

V.M.2.c. Disposition of patent litigation: Approval upon expiration of 30-month stay or 7½ years from date of listed drug approval (§ 314.107(b)(3)(i)). We proposed that a 30-month stay (or a delay in approval for a 7½-year period where applicable) would be available only when the patent owner or exclusive patent licensee initiates a patent infringement action within the statutory timeframe in response to notice of a paragraph IV certification to a patent submitted to FDA before the date on which the 505(b)(2) application or ANDA was submitted (see proposed § 314.107(b)(3)(i)(A) and section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act).

We proposed to clarify that a 30-month stay (or 7½ years where applicable) begins on the later of the date of receipt of the notice of paragraph IV certification by any owner of the listed patent, the NDA holder who is an exclusive patent licensee, or its representative(s) (see proposed § 314.107(b)(3)(i)(A)). In the proposed rule, we noted that a period of pediatric exclusivity under section 505A of the FD&C Act also may affect the timing of approval of a 505(b)(2) application or ANDA in the circumstances described in proposed § 314.107(b)(3) (see 80 FR 6802 at 6863).

In the following paragraphs, we discuss a comment on proposed § 314.107(b)(3)(i). After considering this comment, we are finalizing proposed § 314.107(b)(3)(i) with the IRTNMTA-related revisions described in section V.A.3 and a revision to conform with § 314.107(f)(1) and clarify that a 30-month stay begins on the later of the date of receipt of the notice of paragraph IV certification by any owner of the listed patent, the NDA holder, or its representative(s). We also are making a technical amendment to the paragraph heading described in section V.P.3.

(Comment 53) One comment recommended that FDA revise § 314.107(b)(3)(i) to accept any reason a court provides for reducing the 30-month stay, and not solely an extension or reduction of the 30-month stay because of a failure of the applicant or patent owner to cooperate reasonably in expediting the action.

(Response 53) We agree that if, before the expiration of the stay, the court enters an order requiring the 30-month or 7½-year period to be terminated, the 505(b)(2) application or ANDA may be approved in accordance with the court's order (see § 314.107(b)(3)(vii) and section V.M.2.i). However, we are not revising the regulation because § 314.107(b)(3)(vii) adequately addresses the concern described in the comment by providing for termination of the

30-month stay if the court enters an order requiring the 30-month stay to be terminated. Our regulation governing this scenario is consistent with the statutory purpose of the stay, which allows time for claims of patent infringement to be litigated prior to approval of the potentially infringing drug product.

V.M.2.d. Federal district court decision of invalidity, unenforceability, or non-infringement (§ 314.107(b)(3)(ii)). The MMA amended section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act to describe certain types of court decisions in patent litigation that will terminate a 30-month stay (or 7½ years where applicable) and lead to approval of a 505(b)(2) application or ANDA that is otherwise eligible for approval. We proposed to revise our regulations to implement section 505(c)(3)(C)(i) and (j)(5)(B)(iii)(I) of the FD&C Act by providing that if, before the expiration of the 30-month stay (or 7½ years where applicable), the district court decides that the patent is invalid, unenforceable, or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the 505(b)(2) application or ANDA may be approved on the date on which the court enters judgment reflecting the decision pursuant to Federal Rule of Civil Procedure (Fed. R. Civ. P.) Rule 58, or the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed (see proposed § 314.107(b)(3)(ii)). We also proposed that a Federal district court decision that the applicable patent is unenforceable (for example, because of inequitable conduct in patent prosecution) would terminate a 30-month stay or 7½ years where applicable (see proposed § 314.107(b)(3)(ii)).

We received no comments on these proposed revisions. We are finalizing proposed § 314.107(b)(3)(ii) with a technical amendment to add the term “unenforceable” to § 314.107(b)(3)(ii)(B) for consistency and completeness.

V.M.2.e. Appeal of Federal district court judgment of infringement

(§ 314.107(b)(3)(iii)). We proposed to revise our regulations to implement section 505(c)(3)(C)(ii)(I) and (j)(5)(B)(iii)(II)(aa) of the FD&C Act by providing that if, before the expiration of the 30-month stay (or 7½ years where applicable), the Federal district court decides that the patent has been infringed and the judgment is appealed, the 505(b)(2) application or ANDA may be approved on: (1) The date on which the mandate is issued by the court of appeals entering judgment that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity) or (2) the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed.

We received no comments on these proposed revisions. We are finalizing proposed § 314.107(b)(3)(iii) with technical amendments to add the term “unenforceable” to § 314.107(b)(3)(iii)(A) and (B) for consistency and completeness. We are also deleting the parenthetical reference to a substantive determination by a Federal district court that there is no cause of action for patent invalidity for the reason discussed in section V.M.2.d.

V.M.2.f. Affirmation or non-appeal of Federal district court judgment of infringement

(§ 314.107(b)(3)(iv)). We proposed to establish a regulation that would implement section 505(c)(3)(C)(ii)(II) and (j)(5)(B)(iii)(II)(bb) of the FD&C Act by providing that if, before the expiration of the 30-month stay (or 7½ years where applicable), the Federal district court decides that the patent that is the subject of the paragraph IV certification is infringed and this judgment is not appealed or is affirmed on appeal, the 505(b)(2) application or ANDA may be approved no earlier than the date specified by the district court in an order under 35 U.S.C. 271(e)(4)(A) (see proposed § 314.107(b)(3)(iv)). We proposed to clarify that the 505(b)(2) application or ANDA

may be approved no earlier than the date specified by the district court in a 35 U.S.C. 271(e)(4)(A) order because the order may not take into account any other unexpired patents or unexpired exclusivity (or deficiencies in the application) that would delay approval of the 505(b)(2) application or ANDA beyond the expiration date of the infringed patent (see proposed § 314.107(b)(3)(iv)). In the following paragraphs, we discuss a comment related to this provision. After considering this comment, we are finalizing proposed § 314.107(b)(3)(iv) without change.

(Comment 54) One comment recommends that FDA revise § 314.107(b)(3) to provide that FDA will not approve a pending 505(b)(2) application or ANDA if a district court decides after the 30-month stay or 7½-year period has expired that the patent that is the subject of the paragraph IV certification is infringed. The comment expresses concern that the regulatory focus on court decisions before the expiration of the 30-month stay or 7½-year period may be interpreted to mean that FDA can approve a 505(b)(2) application or ANDA if a district court decides after the 30-month stay or 7½-year period has expired that the proposed product would infringe a listed patent.

(Response 54) We decline to revise § 314.107(b)(3) as suggested because other regulations address the concern described in the comment (see, e.g., §§ 314.50(i)(6)(i) and 314.94(a)(12)(viii)(A) (requiring a 505(b)(2) or ANDA applicant to amend a previously submitted paragraph IV certification after a finding of patent infringement)). We are enhancing our regulations to impose a duty on 505(b)(2) and ANDA applicants to notify FDA of any court judgment, settlement order, or consent decree regarding a patent described in § 314.107(b)(3) (see § 314.107(e)(1)(i); see also § 314.107(e)(1)(ii)). We are also requiring an applicant to submit a copy of any court order under 35 U.S.C. 271(e)(4)(A) providing that the 505(b)(2)

application or ANDA may be approved no earlier than the date specified in the order, irrespective of whether the injunction relates to a patent described in § 314.107(b)(3), within 14 days of the court's entry of the order (see § 314.107(e)(1)(vi)). In addition, the Agency routinely contacts an applicant after the 30-month stay (or 7½ years where applicable) has expired to confirm the status of any pending litigation prior to an action on the 505(b)(2) application or ANDA.

V.M.2.g. Grant of preliminary injunction by Federal district court (§ 314.107(b)(3)(v)).

We proposed to revise our regulations to implement section 505(c)(3)(C)(iii) and (iv) and (j)(5)(B)(iii)(III) and (IV) of the FD&C Act by providing that if a preliminary injunction is entered before the expiration of the 30-month stay (or 7½ years where applicable), the stay of approval would be extended until the court decides the issues of patent infringement and validity. In the proposed rule, we explained that proposed § 314.107(b)(3)(v) cross-references the applicable paragraph of § 314.107(b)(3) that would address the timing of approval of the 505(b)(2) application or ANDA based on the court's decision regarding patent validity and infringement. We proposed that if the court later decides that the patent is invalid, unenforceable, or not infringed, the 505(b)(2) application or ANDA may be approved as provided in § 314.107(b)(3)(iii) or (iv), whichever is applicable (see proposed § 314.107(b)(3)(v)). In addition, we proposed to clarify that the court referred to in § 314.107(b)(3)(v) is the Federal district court hearing the patent infringement action.

In the following paragraphs, we discuss two comments on the timing of approval of a 505(b)(2) application or ANDA after a preliminary injunction has been entered. After considering these comments, we are revising § 314.107(b)(3)(v) to more clearly describe the timing of approval of a 505(b)(2) application or ANDA when a preliminary injunction is entered

before the expiration of a 30-month stay (or 7½ years where applicable) and to cross-reference the applicable paragraphs of § 314.107(b)(3). We are redesignating a portion of proposed § 314.107(b)(3)(v) as paragraph (b)(3)(v)(A) and adding paragraph (b)(3)(v)(B) to implement section 505(c)(3)(C)(iv) and (j)(5)(B)(iii)(IV) of the FD&C Act. With these revisions, the regulation provides:

- If a preliminary injunction is entered before the expiration of a 30-month stay (or 7½ years where applicable) and the Federal district court later decides that the patent is invalid, unenforceable, or not infringed, the 505(b)(2) application or ANDA may be approved as provided in § 314.107(b)(3)(ii) (see § 314.107(b)(3)(v)(A) and section 505(c)(3)(C)(iii) and (j)(5)(B)(iii)(III) of the FD&C Act).
- If a preliminary injunction is entered before the expiration of a 30-month stay (or 7½ years where applicable) and the Federal district court later decides that the patent is infringed, the 505(b)(2) application or ANDA may be approved as provided in § 314.107(b)(3)(iii) or (iv), whichever is applicable (see § 314.107(b)(3)(v)(B) and section 505(c)(3)(C)(iv) and (j)(5)(B)(iii)(IV) of the FD&C Act).

(Comment 55) One comment asserts that if a preliminary injunction is entered before the expiration of the 30-month stay, the stay should not be extended until the court decides the issues of patent infringement and validity because the preliminary injunction serves the purpose of the stay. The comment recommends that FDA issue a final approval of the 505(b)(2) application or ANDA (if otherwise eligible for approval) after the 30-month stay expires so that the product can be marketed without delay at such time as the injunction is lifted.

(Response 55) We disagree with the comment. If a preliminary injunction is entered before the expiration of the 30-month stay (or 7½ years where applicable), FDA interprets



section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act to require an extension of the stay until the court decides the issues of patent infringement and validity because all of the outcomes described in the statute presume that approval will not occur until a later date.

(Comment 56) One comment requests that FDA revise the regulation to clarify the timing of approval if the district court enters a preliminary injunction after the 30-month stay expires. The comment recommends that FDA not approve a pending 505(b)(2) application or ANDA in this scenario unless the court later decides the patent is invalid, unenforceable, or not infringed. The comment also asserts that FDA's view that a preliminary injunction entered before the expiration of the 30-month stay would extend the stay until the court decides the issues of patent infringement and validity suggests that the issuance of a preliminary injunction after expiry of the 30-month or 7½-year period, combined with a district court finding of infringement, stays approval through at least the appeal.

(Response 56) We decline to adopt the recommendations in the comment. It is unnecessary for FDA to establish a regulation that addresses the timing of approval of a 505(b)(2) application or ANDA if a district court enters a preliminary injunction after the 30-month stay (or 7½-year period where applicable) has expired. If a party to a patent infringement action involving a patent described in § 314.107(b)(3) seeks to ensure that a 505(b)(2) application or ANDA is not approved while the litigation is pending, the party may request a preliminary injunction before the 30-month stay (or 7½-year period where applicable) expires. If a court enters a preliminary injunction after the 30-month stay (or 7½-year period where applicable) has expired, parties should ensure that the court specifies the duration and effect of the injunction.

(Comment 57) One comment suggests that if a court requests an applicant to voluntarily agree not to begin marketing the drug product or to provide pre-launch notice instead of issuing a preliminary injunction, FDA should treat these agreements as equivalent to a preliminary injunction and similarly extend the 30-month stay or 7½-year period.

(Response 57) We decline to adopt this suggestion. The FD&C Act provides that if the district court grants a preliminary injunction before the expiration of the 30-month stay (or 7½ years where applicable) to preserve the status quo until the court decides the issues of patent infringement and validity, the stay must be extended until the applicable date described in section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act. A voluntary agreement not to begin marketing the drug product or to provide pre-launch notice does not fall within this statutory exception to the termination of the stay at the end of the 30-month period (or 7½ year-period where applicable). Accordingly, we do not consider such agreements to be equivalent to a preliminary injunction for purposes of extending the stay. Moreover, it is unnecessary for the Agency to address these circumstances through regulation because the parties to the litigation can specify the desired terms of the agreement.

V.M.2.h. Written consent to approval by patent owner or exclusive patent licensee (§ 314.107(b)(3)(vi)). We proposed to clarify that if the patent owner or exclusive patent licensee (or their representatives) agreed in writing that the 505(b)(2) application or ANDA may be approved, the 30-month stay (or 7½ years where applicable) would be terminated and the approval may be granted on or after the date of the consent (see proposed § 314.107(b)(3)(vi)). In the proposed rule, we noted that this scenario may arise, for example, if settlement of the patent litigation results in a license to the 505(b)(2) or ANDA applicant. One comment agrees with the addition of this provision because it expressly permits the party that receives the benefit

of the statutory 30-month stay to waive that benefit. We agree with the comment and we are finalizing proposed § 314.107(b)(3)(vi) without change.

V.M.2.i. Court order terminating 30-month or 7½-year period (§ 314.107(b)(3)(vii)).

We proposed to clarify that if a court enters an order requiring the termination of the 30-month stay (or 7½ years where applicable), the 505(b)(2) application or ANDA, if otherwise eligible for approval, may be approved in accordance with the court order (see proposed § 314.107(b)(3)(vii)). We received no comments on this provision, and we are finalizing proposed § 314.107(b)(3)(vii) without change.

V.M.2.j. Court order of dismissal without a finding of infringement (§ 314.107(b)(3)(viii)). We proposed to codify FDA's policy that a Federal district court's entry of an order of dismissal, with or without prejudice, of patent infringement litigation that was timely initiated in response to the 505(b)(2) or ANDA applicant's notice of a paragraph IV certification will terminate the 30-month period (or 7½ years where applicable) if such order does not state a finding of patent infringement (see proposed § 314.107(b)(3)(viii)).

In the following paragraphs, we discuss two comments on proposed § 314.107(b)(3)(viii). After considering these comments, we are revising § 314.107(b)(3)(viii) to clarify that the 30-month period (or 7½ years where applicable) will be terminated if the court(s) enter(s) an order of dismissal without a finding of infringement in each pending suit for patent infringement brought within 45 days of receipt of the notice of paragraph IV certification sent by the 505(b)(2) or ANDA applicant.

(Comment 58) One comment opines that proposed § 314.107(b)(3)(viii) should be withdrawn because the statute does not specify that an order of dismissal without a finding of

infringement will terminate a 30-month stay (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the FD&C Act).

(Response 58) We decline to withdraw our proposal. The MMA's amendments to the FD&C Act clarify the timing of approval of a 505(b)(2) application or ANDA, respectively, in relation to a settlement order or consent decree stating that the patent that is the subject of the paragraph IV certification is invalid or not infringed (see section 505(c)(3)(C)(i)(II), (c)(3)(C)(ii)(I)(bb), (j)(5)(B)(iii)(I)(bb), and (j)(5)(B)(iii)(II)(aa)(BB) of the FD&C Act). However, the MMA does not address whether a 30-month stay may be terminated and a 505(b)(2) application or ANDA may be approved if the court enters an order of dismissal without a finding of patent infringement. Because this issue was not addressed by Congress, the Agency is using its authority to establish rules for the efficient enforcement of the FD&C Act to clarify the effect of a Federal district court's entry of an order of dismissal without a finding of infringement on a 30-month stay of approval. The Agency's approach is consistent with the statutory scheme because it avoids unwarranted delays in approval of a 505(b)(2) application or ANDA while protecting innovator intellectual property rights. As we explained in the proposed rule, it is appropriate that a 30-month stay be terminated under these circumstances because the statutory purpose of the stay is to allow time for claims of patent infringement to be litigated prior to approval of the potentially infringing drug product. If the patent owner or exclusive patent licensee dismisses the patent infringement action on terms that the court considers proper (see Fed. R. Civ. P. Rule 41(a)(2)), then there should be no further delay of approval of a 505(b)(2) application or ANDA otherwise eligible for approval.

(Comment 59) One comment recommends that FDA revise proposed § 314.107(b)(3)(viii) to exclude dismissals that do not terminate all timely filed litigation with

respect to the patent(s) in suit. The comment explains that parallel suits for patent infringement may be filed in different Federal district courts within the 45-day period described in section 505(j)(5)(B)(iii) of the FD&C Act, and one or more suits may be dismissed because of lack of jurisdiction or other reasons. The comment maintains that the 30-month stay should remain in effect if one of multiple patent infringement actions filed in response to notice of a paragraph IV certification is dismissed while at least one of the timely filed lawsuits continues to be litigated.

(Response 59) We agree that the 30-month stay should remain in effect if a patent infringement action that was timely filed in response to a paragraph IV certification continues to be litigated after the dismissal of a parallel action. We are revising § 314.107(b)(3)(viii) to clarify that the 30-month period (or 7½ years where applicable) will be terminated if the court(s) enter(s) an order of dismissal without a finding of infringement in each pending suit for patent infringement brought within 45 days of receipt of the notice of paragraph IV certification sent by the 505(b)(2) or ANDA applicant.

(Comment 60) One comment recommends that FDA revise proposed § 314.107(b)(3)(viii) to provide that if the court enters an order of dismissal without a finding of patent infringement based on an agreement not to make or sell the drug until a specified future date, the stay should continue until the date provided in the agreement.

(Response 60) We decline to adopt this suggestion. If the court(s) enter(s) an order of dismissal without a finding of infringement in each pending suit for patent infringement brought within 45 days of receipt of the notice of paragraph IV certification sent by the 505(b)(2) or ANDA applicant, FDA may approve the 505(b)(2) application or ANDA on or after the date of the order. If a 505(b)(2) or ANDA applicant has entered into an agreement not to make or sell

the drug until a specified future date and the 505(b)(2) application or ANDA receives final approval, the applicant can choose not to make or sell the product until the specified date.

#### V.M.3. Timing of Approval of Subsequent ANDA (§ 314.107(c))

We proposed to revise § 314.107(c) to remove provisions that have been superseded by the FD&C Act as revised by the MMA and to generally conform with the FD&C Act. We proposed to revise § 314.107(c)(1) to incorporate the statutory term “first applicant” and to distinguish a “first applicant” from a “subsequent applicant” (see section 505(j)(5)(B)(iv)(II)(bb) of the FD&C Act and proposed § 314.3(b)). We proposed that an ANDA has been submitted by a subsequent applicant if the ANDA has not been submitted by a first applicant and contains a paragraph IV certification to a relevant patent that has been listed for the drug product for which a first applicant has submitted an ANDA (see proposed § 314.107(c)(1)). We proposed that a subsequent applicant’s ANDA will not be approved during the period when any first applicant for the drug product is eligible for 180-day exclusivity or during the 180-day exclusivity period of any first applicant (see proposed § 314.107(c)(1) and section 505(j)(5)(B)(iv)(I) of the FD&C Act).

We proposed to delete the definition of the “applicant submitting the first application” in existing § 314.107(c)(2) because it was superseded by the statutory definition of “first applicant” added by the MMA. We also proposed to delete § 314.107(c)(3), which described the potential consequences of a first applicant’s failure to actively pursue approval of its ANDA (see section 505(j)(5)(D) of the FD&C Act).

We proposed to revise § 314.107(c)(4) (redesignated as proposed § 314.107(c)(2)) to conform with the statutory change to the event that triggers the start of the 180-day exclusivity period for a first applicant (see section 505(j)(5)(B)(iv)(I) of the FD&C Act). Given that the

180-day exclusivity period begins on the date of the first commercial marketing of the drug product (including the commercial marketing of the listed drug) by any first applicant, we proposed to require a first applicant to submit correspondence to its ANDA notifying FDA within 30 days of the date of first commercial marketing of the drug product (see proposed § 314.107(c)(2) and section 505(j)(5)(B)(iv)(I) of the FD&C Act). If the first applicant does not notify FDA within this timeframe, we proposed to deem the date of first commercial marketing to be the date of the ANDA's approval. In the proposed rule, we noted that this may have the effect of shortening the 180-day period of exclusivity in a manner similar to existing § 314.107(c)(4). We also proposed to remove the description of "commercial marketing" from § 314.107(c)(4) because we proposed to define "commercial marketing" in proposed § 314.3(b) with certain modifications to the scope of the exclusion for transfer of the drug product for reasons other than sale.

In the following paragraphs, we discuss three comments on proposed § 314.107(c). After considering these comments, we are finalizing proposed § 314.107(c)(1) without change and we are finalizing proposed § 314.107(c)(2) with a technical amendment to include a reference to first commercial marketing of the RLD for consistency with section 505(j)(5)(B)(iv)(I) of the FD&C Act. We also are making an editorial correction to remove the introductory phrase in § 314.107(c)(2) referring to § 314.107(c)(1). We are not finalizing our proposal to delete § 314.107(c)(3) because we want to retain flexibility to ensure that approval of ANDAs of subsequent applicants is not blocked, for example, by a first applicant that is nonresponsive to repeated inquiries from the Agency regarding its ANDA. In addition, we are making clarifying revisions to this provision. As revised, § 314.107(c)(3) explains that if FDA concludes that a

first applicant is not actively pursuing approval of its ANDA, FDA may immediately approve an ANDA(s) of a subsequent applicant(s) if the ANDA(s) is otherwise eligible for approval.

(Comment 61) One comment asserts that FDA's proposal to deem the date of first commercial marketing to be the date of the drug product's approval if a first applicant fails to timely notify FDA is inconsistent with the statute, FDA's proposed and existing definitions of "commercial marketing," and the predecessor regulation at § 314.107(c)(3), because the product was not actually marketed on the deemed date. Another comment maintains that FDA's proposal to deem the date of first commercial marketing to be the date of the drug product's approval if a first applicant fails to timely notify FDA is a penalty that is not warranted by the statutory change in the commercial marketing trigger of the 180-day exclusivity period.

(Response 61) We do not find these comments persuasive. Section 505(j)(5)(B)(iv)(I) of the FD&C Act provides that the period of 180-day exclusivity will begin on the date of the first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant. This commercial marketing trigger differs from the version of section 505(j)(5)(B)(iv)(I) in effect prior to enactment of the MMA, which provided that the 180-day exclusivity period will begin on the earlier of two events, one of which was the date the Secretary receives notice from the applicant of the first commercial marketing of the drug eligible for 180-day exclusivity. Based on the change in the commercial marketing trigger from the date on which FDA receives notice from the applicant of the first commercial marketing to the date of the first commercial marketing of the drug, we are requiring the first applicant to notify FDA within 30 days of the date of first commercial marketing. This requirement is intended to facilitate the efficient enforcement of the FD&C Act and provide FDA with adequate notice to inform the timing of approval for ANDAs submitted by subsequent applicants. If a first



applicant does not notify FDA within this timeframe, we will deem the date of first commercial marketing to be the date of the ANDA's approval. This consequence of a first applicant's failure to provide timely notification to FDA is similar to the consequence described in the predecessor regulation at § 314.107(c)(4), which provided that if an applicant does not promptly notify FDA of commercial marketing, the effective date of approval shall be deemed to be the date of the commencement of first commercial marketing. We expect that the regulation will encourage first applicants to provide timely notification to FDA. Given that the date of notification is within a first applicant's control, we expect that there will be few instances in which there is a need to deem the date of first commercial marketing to be the date of the ANDA's approval.

(Comment 62) One comment expresses concern that FDA may deem the date of first commercial marketing to be the date of the drug product's approval if a first applicant does not launch its drug product within 30 days after ANDA approval. The comment proposes that FDA require a first applicant to notify FDA if the applicant will not launch the drug product within 30 days after ANDA approval, but intends to launch the drug product within 75 days after ANDA approval.

(Response 62) We decline to adopt this suggestion because it is unnecessary. FDA would only deem the date of first commercial marketing to be the date of the ANDA's approval if a first applicant began commercial marketing of the drug product described in the ANDA or of the reference listed drug and failed to notify FDA within 30 days of the first commercial marketing (see § 314.107(c)(2)). This provision would not apply if commercial marketing had not yet commenced. FDA's requirement for a first applicant to timely notify the Agency of the date of first commercial marketing is intended to facilitate implementation of the statutory change in the commercial marketing trigger of the 180-day exclusivity period (section

505(j)(5)(B)(iv)(I) of the FD&C Act). This notification requirement is unrelated to the statutory conditions under which a first applicant would forfeit the 180-day exclusivity period for failure to market the product (see section 505(j)(5)(D)(i)(I) of the FD&C Act). We will determine whether additional rulemaking related to 180-day exclusivity is necessary in the future.

#### V.M.4. Delay of Approval Due to Exclusivity (§ 314.107(d))

We proposed to clarify that approval of a 505(b)(2) application or ANDA may be delayed by orphan drug exclusivity under 21 CFR 316.31 or pediatric exclusivity under section 505A of the FD&C Act, in addition to the exclusivities described in § 314.108 (see proposed § 314.107(d)).

In section V.A.7, we discuss a comment on proposed § 314.107(d) (see Comment 8). After considering this comment, we are revising § 314.107(d) to indicate that approval of a 505(b)(2) application or ANDA also may be delayed by a period of exclusivity for the listed drug under section 505E of the FD&C Act. We are also making a technical edit to refer to section 527 of the FD&C Act in the context of a delay in approval of a 505(b)(2) application or ANDA because of orphan drug exclusivity.

#### V.M.5. Notification of Court Actions or Written Consent to Approval (§ 314.107(e))

We proposed to revise § 314.107(e) to expand the scope of documentation that an applicant must submit to FDA regarding court actions and settlements related to patents that may affect the timing of approval of a 505(b)(2) application or ANDA. We proposed to require a 505(b)(2) or ANDA applicant to submit a copy of any judgment by the court (Federal district court or mandate of the court of appeals) finding a patent described in § 314.107(b)(3) invalid, unenforceable, or not infringed, or finding the patent valid and infringed (see proposed § 314.107(e)(1)(i)). We also proposed to require a 505(b)(2) or ANDA applicant to submit to

FDA a copy of specified documented agreements and court actions other than judgments to facilitate FDA's administration of the FD&C Act (see § 314.107(e)(1)(i) through (vi)).

We explained that the proposed requirement to submit a copy of any documented agreement described in § 314.107(b)(3)(vi) would require submission of written documentation that the parties have entered into a settlement that terminated the patent infringement litigation, but would not require applicants to send copies of the actual settlement agreement to FDA (see proposed § 314.107(e)(1)(iv)). To ensure timely notification to FDA, we proposed to require a 505(b)(2) or ANDA applicant to submit all required information to the appropriate division in OND or to OGD, within 14 calendar days of the date of entry by the court, the date of appeal or expiration of the time for appeal, or the date of documented agreement, as applicable (see proposed § 314.107(e)(2)).

In the following paragraphs, we discuss a comment on proposed § 314.107(e)(1)(iv). After considering this comment, we are revising § 314.107(e)(1)(iv) to require submission of a copy of any "written consent to approval" by the patent owner or exclusive patent licensee, and we are making a conforming revision to § 314.107(e)(2) and to the paragraph heading for § 314.107(e). We also are clarifying that a copy of any order entered by the court terminating the 30-month or 7½-year period includes an order described in § 314.107(b)(3)(vii) and (viii). Finally, for administrative convenience, we are revising § 314.107(e)(2) to provide that all information required by § 314.107(e)(1) must be sent to the applicant's NDA or ANDA rather than to OGD or the appropriate division in OND.

(Comment 63) One comment agrees with FDA's proposal to require submission of written documentation that the parties have entered into a settlement that has terminated the patent infringement litigation, and recommends that FDA revise proposed § 314.107(e)(1)(iv) to

expressly state that a “documented agreement” does not refer to the settlement agreement, and that a copy of the actual settlement agreement need not be submitted. The comment also requests that FDA clarify the content of the documentation that should be submitted.

(Response 63) We agree that the proposal to require applicants to submit a copy of any “documented agreement” has been the source of confusion, notwithstanding the statement in the proposed rule that applicants are not required to send copies of the actual settlement agreement to FDA. We are revising § 314.107(e)(1)(iv) to require submission of a copy of any “written consent to approval” by the patent owner or exclusive patent licensee. This revision is intended to clarify the requested information and align with the text of § 314.107(b)(3)(vi). A letter to FDA from the patent owner(s) or exclusive patent licensee that provides consent to approval of the 505(b)(2) application or ANDA any time on or after the date of consent would be acceptable. Although FDA does not require a copy of the actual settlement agreement, we note that generic drug applicants are required to file certain agreements with the FTC (see section 1112 of the MMA).

#### V.M.6. Computation of the 45-Day Time Clock (§ 314.107(f))

We proposed to revise § 314.107(f)(1) and (2) to clarify the computation of the 45-day period after receipt of notice of paragraph IV certification and to enhance the requirements for notifying FDA of any legal action filed within this timeframe. We proposed to add § 314.107(f)(2)(iii) to clarify that a 505(b)(2) application or ANDA may be approved upon expiration of the 45-day period (if the 505(b)(2) or ANDA applicant confirms that a legal action for patent infringement has not been filed within the 45-day period) or upon completion of FDA’s review of the 505(b)(2) application or ANDA, whichever is later. We also proposed to revise § 314.107(f)(3) to expressly permit a representative of the patent owner or NDA holder

who is an exclusive patent licensee to waive the opportunity to file a patent infringement action within the 45-day period.

We received no comments regarding these proposed revisions, and we are finalizing proposed § 314.107(f) without change, except for the technical amendments described in section V.P.5 regarding the location to which the notification must be sent.

#### V.M.7. Conversion of Approval to Tentative Approval (§ 314.107(g))

We proposed to add § 314.107(g) to clarify that if FDA issues an approval letter in error or a court enters an order requiring that the date of approval be delayed for an already approved 505(b)(2) application or ANDA, FDA will convert the approval to a tentative approval if appropriate. In the following paragraphs, we discuss a comment on this proposed provision. After considering this comment, we are finalizing proposed § 314.107(g) without change.

(Comment 64) One comment recommends that FDA remove the qualifier “if appropriate” from proposed § 314.107(g). The comment also requests that FDA clarify that “court” refers to either a district court or an appellate court for consistency with Mylan Labs., Inc. v. Thompson, 389 F.3d 1272 (D.C. Cir. 2004).

(Response 64) FDA declines to adopt the suggestion to remove the qualifier “if appropriate” from proposed § 314.107(g) because there are circumstances in which it may not be appropriate to convert an approval to a tentative approval (e.g., a stay of the district court’s order pending appeal). Moreover, the qualifier “if appropriate” also modifies FDA’s issuance of an approval letter in error, and the appropriateness of conversion to tentative approval may depend on a variety of factors. If either a district court or appellate court enters an order requiring that the date of approval of an already approved 505(b)(2) application or ANDA be delayed, FDA will convert the approval to a tentative approval if appropriate.

V.N. Assessing Bioavailability and Bioequivalence for Drugs Not Intended To Be Absorbed Into the Bloodstream (§ 320.23)

We proposed to revise § 320.23 to reflect the MMA's amendments to section 505(j)(8) of the FD&C Act, which permit use of scientifically valid methods for assessing bioavailability and bioequivalence for drugs that are not intended to be absorbed into the bloodstream and essentially codify our existing practice. We received no comments regarding these proposed revisions, and we are finalizing proposed § 320.23 without change.

V.O. Miscellaneous

We proposed several clarifying revisions and editorial changes throughout the sections of parts 314 and 320 that were the subject of the proposed rule. These changes were intended to promote consistency throughout our regulations, incorporate "plain language," employ grammatically correct phrasing, and otherwise clarify the text of these regulations. We also proposed certain revisions to provisions that contemplated the submission of paper to facilitate the transition to electronic submissions in the future. We did not receive any comments on these proposed revisions, and we are finalizing them without change.

V.P. Technical Amendments

We are making several technical amendments in the sections of parts 314 and 320 that are the subject of this rulemaking. These changes are intended to promote clarity and consistency throughout our regulations and correct certain outdated or incorrect information. Examples of revisions that are not otherwise described are provided in sections V.P.1 through V.P.6.

V.P.1. Consistent Use of Defined Terms

We are replacing the terms “application” and “abbreviated application” with the commonly used abbreviations “NDA” and/or “ANDA,” as appropriate, in the following sections: §§ 314.3(b) (definitions of “original application or original NDA” and “tentative approval”); 314.50(h); 314.53(b)(1); 314.93(b); 314.94(a)(3), (a)(12)(i)(A)(4)(i), (a)(12)(ii), (a)(12)(viii)(B), and introductory text to § 314.94; 314.95(d)(1) and (f); 314.97(a); 314.107(b)(4) and (f)(3); and 314.127(a)(2) and (a)(8)(ii)(B) and (C).

We are replacing the term “act” with “Federal Food, Drug, and Cosmetic Act” in the following sections: §§ 314.50(d); 314.60(b)(1) and (4), (c)(1)(i), and (c)(2); 314.93(d)(3) and (e)(1)(iii)(C); 314.94(a)(3)(ii), (a)(5)(ii)(A), (a)(7)(ii)(C), and (a)(8)(iv); 314.125(a) and (b)(2), (11), and (18); and 314.127(a)(3)(iii)(A)(2) and (a)(12).

We are defining “Agency” as an alternate term for “FDA” for clarity (see § 314.3(b)).

We are replacing references to the “holder of [an or the] approved application” with the defined term “NDA holder” in the following sections: §§ 314.50(i)(1)(i)(A)(4)(ii); 314.70(a)(2); and 314.94(a)(12)(i)(A)(4)(ii).

We are revising the proposed definition of “resubmission” in § 314.3(b) to clarify that the definition applies only in the context of a complete response letter (compare § 314.101(b)(3)(ii), which uses the term “resubmit” with a different meaning and in a different context).

We are replacing the term “right of reference” with the defined term “right of reference or use” in § 314.60(c)(1)(iii).

We are making an editorial correction to the proposed definition of “therapeutic equivalents” in § 314.3(b) to combine the sentences into a single-sentence definition to be consistent with the definition in the Orange Book. As revised, “therapeutic equivalents” are approved drug products that are pharmaceutical equivalents for which bioequivalence has been

demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

We are replacing the reference to a “use patent” with the term “method-of-use patent” (see §§ 314.50(i)(1)(iii)(A) and (B), 314.52(a)(3), 314.53(e), 314.94(a)(12)(iii)(A) and (B), and 314.95(a)(3)).

#### V.P.2. Alignment of Certain Regulations for 505(b)(2) Applications and ANDAs

We are making conforming revisions between certain provisions in §§ 314.50 and 314.94 to align the requirements for 505(b)(2) applications and ANDAs and enhance clarity.

We are expressly providing, with respect to a 505(b)(2) applicant that amends its paragraph IV certification after a finding of patent infringement, that once an amendment for the change has been submitted, the 505(b)(2) application will no longer be considered to contain a paragraph IV certification to the patent (see § 314.50(i)(6)(i)). However, we explain that if a final decision finds the patent to be invalid and infringed, an amended certification is not required. This revision to § 314.50(i)(6)(i) corresponds to the parallel regulation for ANDAs in § 314.94(a)(12)(viii)(A) and clarifies the general statement in the introductory text of § 314.50(i)(6) regarding amended patent certifications for 505(b)(2) applications.

We are revising § 314.94(a)(12)(viii)(A) to expressly provide that, after a finding of patent infringement, an ANDA applicant must submit a paragraph III certification or, with respect to a method-of-use patent, the applicant may instead provide a statement under § 314.94(a)(12)(iii) if the applicant amends its ANDA such that the applicant is no longer seeking approval for a method of use claimed by the patent. This revision to § 314.94(a)(12)(viii)(A) corresponds to the parallel regulation for 505(b)(2) applications in § 314.50(i)(6)(i) and describes an acceptable approach under the statute and existing regulations.



We are revising §§ 314.50(i)(1)(i)(A)(4)(ii) and 314.94(a)(12)(i)(A)(4)(ii) to conform with §§ 314.52(a)(2) and 314.95(a)(2), respectively, and provide that if the NDA holder does not reside or maintain a place of business in the United States, notice of a paragraph IV certification must be sent to its attorney, agent, or other authorized official.

We are revising § 314.94(a)(12)(viii) to clarify that a patent certification or statement may be amended at any time “before the approval of the ANDA,” rather than “before the date of approval of the ANDA” for consistency with § 314.50(i)(6).

#### V.P.3. Technical Corrections to Regulatory Concepts

We are revising the definition of “505(b)(2) application” to clarify that it is an NDA for which “at least some of” the investigations relied upon by the applicant for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (see § 314.3(b)).

We are replacing the term “filed” with “submitted” in the first sentence of § 314.50(i)(4)(ii) to use consistent terminology in this paragraph and to accurately describe FDA’s longstanding practice. As revised, an applicant whose 505(b)(2) application is submitted after the NDA holder’s untimely filing of patent information must submit an appropriate patent certification or statement as to that patent.

We are deleting the phrase “or changed” from §§ 314.50(i)(5) and 314.94(a)(12)(vii) because a 505(b)(2) or ANDA applicant must submit an appropriate patent certification or statement for changes to patent information that are timely filed. We also are changing “each relevant patent” to “each listed patent” in §§ 314.50(i)(5) and 314.94(a)(12)(vii) for clarity.

We are revising the titles of §§ 314.52 and 314.95 to clarify that these sections relate to a notice of certification of invalidity, unenforceability, or non-infringement of a patent, as reflected in the text of these sections and FDA's definition of a paragraph IV certification.

We are revising the paragraph headings of §§ 314.52(f) and 314.95(f) to change them from "Approval" to "Forty-five day period after receipt of notice" to more clearly describe the content of these sections. We are also revising §§ 314.52(f) and 314.95(f) to add the NDA holder's attorney, agent, or other authorized official as potential recipients of the 505(b)(2) or ANDA applicant's notice of paragraph IV certification for consistency with §§ 314.52(a)(2) and 314.95(a)(2).

We are changing "a drug product" to "the drug product" in § 314.53(b)(1) to clarify that for patents that claim a drug product, the applicant must submit information only on those patents that claim the drug product, as is defined in § 314.3, that is described in the pending or approved NDA.

We are revising the description of required patent information for drug substance patents to clarify that information must include whether the patent claims "a" drug substance that is "an" active ingredient in the drug product described in the NDA or supplement to reflect submission of patent information on drug products that contain more than one active ingredient (see § 314.53(c)(2)(i)(M)(1) and (c)(2)(ii)(N)(1)).

We are deleting the phrase "including a 505(b)(2) application" in § 314.53(d)(1) because the provision refers to an original NDA, which describes "stand-alone" applications submitted under section 505(b)(1) of the FD&C Act and 505(b)(2) applications.

We are adding the word “active” to a parenthetical reference to “ingredient” for clarity and consistency with the regulations governing submission of patent information on drug substances (see § 314.53(d)(1)).

We are replacing a reference to the provisions regarding “untimely filed patents” with the phrase “untimely filed patent information” for consistency with the paragraph headings of §§ 314.50(i)(4) and 314.94(a)(12)(vi) (see § 314.53(d)(3)).

We are replacing a reference to a request to “delist a patent” with the phrase “remove a patent from the list” for clarity (see § 314.53(f)(2)(iv)).

We are replacing a reference to an “NDA” in § 314.60(a) with a reference to an “NDA, supplement, or resubmission” for clarity and consistency with the content of this regulation.

We are replacing the phrase “the listed drug approved in the petition” in § 314.93 with the phrase “the listed drug referenced in the approved petition” for accuracy (see § 314.94(a)(3)(i)).

We are revising the paragraph heading of § 314.94(a)(12)(i) to describe “patents claiming drug substance, drug product, or method of use” for clarity and consistency with the regulation.

We are deleting the word “who” in the phrase “letter acknowledging receipt by the person who provided the notice” because the letter described in § 314.95(e) must acknowledge receipt by the person who received the notice, not the person who provided the notice.

We are deleting the phrase “for the active moiety” in the phrase “[s]ubmission of a 505(b)(2) application or an ANDA for the active moiety” because applicants submit 505(b)(2) applications and ANDAs for drug products, not active moieties, and the restriction on submission is described in the cited statutory references (see § 314.101(e)(2)).

We are revising the paragraph heading of § 314.107(b)(3)(i) to refer to the date of “listed drug approval” rather than the “reference product approval” because a 505(b)(2) application or ANDA may rely on a listed drug approved under the FD&C Act.

We are revising § 314.94(a)(12)(viii)(B) to clarify that if removal of a patent from the list results in there being no patents listed for the listed drug identified in the ANDA, the applicant must submit an amended certification reflecting that there are “no relevant patents,” rather than “no listed patents,” to incorporate the terminology used in § 314.94(a)(12)(ii).

We are revising the reference to an approval that “will become effective” to an approval that “will occur” because the Agency no longer uses this terminology (see § 314.108(b)(3)).

#### V.P.4. Technical Corrections to Statutory or Regulatory References

We are correcting statutory and regulatory citations in the sections of part 314 and 320 that are the subject of this rulemaking, as illustrated by the following examples:

- Delete the reference to “section 505 of the act” as unnecessary in the context of an approved NDA (see § 314.70(a)(2));
- Correct the statutory reference to the definition of “new drug” in section 201(p) of the FD&C Act (21 U.S.C. 321(p)) (see § 314.93(d)(3));
- Change “section 505(j)(4)(D)” to “section 505(j)(5)(F)” of the FD&C Act to correctly cite the relevant exclusivity provision (see § 314.94(a)(3)(ii));
- Update the citation for the definition “same drug product formulation” from § 320.1(g) to § 314.3(b) to reflect the relocation of the definition (see § 314.94(a)(7)(i));
- Add a reference to § 314.94(a)(12)(iii) to align with text regarding an ANDA applicant’s submission of an appropriate patent certification or statement (see § 314.94(a)(12)(i)(B) and (a)(12)(viii)(C)(1)(ii));

- Change “section 505(j)(4)(B)(iii)” to “section 505(j)(5)(B)(iii)” of the FD&C Act to correctly cite the statutory provision regarding the 45-day period after receipt of notice of a paragraph IV certification (see § 314.95(f)); and
- Revise § 314.105(a) regarding approval of an NDA to delete the reference to § 314.107(c), which only applies to ANDAs.

#### V.P.5. Changes to Location for Sending Information

We are revising §§ 314.52(a)(2) and 314.95(a)(2) to clarify that the name and address of the NDA holder or its attorney, agent, or authorized official may also be obtained by sending an electronic communication to the Orange Book staff. As revised, §§ 314.52(a)(2) and 314.95(a)(2) provide that this information may be obtained by sending a written or electronic communication to the Orange Book Staff, Office of Generic Drugs, 7620 Standish Pl., Rockville, MD 20855, or to the Orange Book Staff at the email address listed on the Agency’s Web site at <http://www.fda.gov>.

We are revising § 314.53(c)(2)(i)(B) and (c)(2)(ii)(B) to request the NDA applicant’s full address, phone number, and, if available, fax number and email address in addition to the applicant’s name to facilitate communication.

We are revising § 314.107(f)(2) to clarify that notification of the filing of any legal action within 45 days of the receipt of notice of a paragraph IV certification must be sent by a 505(b)(2) applicant to its NDA (rather than to the appropriate OND Review Division) and must be sent by an ANDA applicant to its ANDA (rather than to OGD).

#### V.P.6. Grammatical Corrections

We are making certain revisions to correct or improve grammar or punctuation in the sections of parts 314 and 320 that are the subject of this rulemaking, as illustrated by the following examples:

- Change “which” to “that” (see §§ 314.50(i)(1)(i)(A)(4)(ii) and 314.95(a)(1));
- Change “method of use patent” to “method-of-use patent” (see §§ 314.50(i)(1)(iii) and 314.94(a)(12)(iii));
- Change “[o]nce an amendment for the change in certification has been submitted” to “[o]nce an amendment is submitted to change the certification” (see § 314.50(i)(6));
- Change “will no longer be considered to be one containing” to “will no longer be considered to contain” (see §§ 314.50(i)(6) and 314.94(a)(12)(viii)(A) and (B));
- Delete the word “use” in the phrase “one or more methods of using the drug product for which use approval is being sought” for clarity (see § 314.53(c)(2)(i)(O)(1));
- Change “United States” to “U.S.” (see § 314.53(c)(2)(ii)(H));
- Change “shall” to “must” as appropriate (see §§ 314.53(d)(1) and 314.94(a), (a)(1), (a)(12)(i)(A)(4)(i) and (ii), (b), and (d)(2));
- Change “except that § 314.50(d)(1)(ii)(c) must contain” to “except that the [technical] section described in § 314.50(d)(1)(ii)(c) must contain” or “except that the information required under § 314.50(d)(1)(ii)(c) must contain” for clarity (see §§ 314.54(a)(2) and 314.94(a)(9)(i));
- Change “any bioavailability of bioequivalence testing” to “any bioavailability or bioequivalence testing” to correct a typographical error (see § 314.94(a)(7)(ii));
- Change “it” to “the study” for clarity (see §§ 314.94(a)(7)(iii)(B) and 314.101(d)(6) and (7));

- Change “amendment to § 314.94(a)(9)” to “amendment under § 314.94(a)(9)” for clarity (see § 314.96(b));
- Change “their representatives” to “its representative” or “its representative(s)” (see §§ 314.94(a)(12)(i)(A)(4)(ii) and 314.107(f)(2)(ii) and (iii) and (f)(3));
- Delete the words “is or” from the phrase “is or has been removed” (see § 314.94(a)(12)(viii)(B)); and
- Add appropriate descriptors (e.g., “section” and “paragraph”) to modify statutory and regulatory references (see § 314.94(d)(2)).

#### VI. Effective Date

This final rule is effective [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. The final rule applies to any new submission (including but not limited to an NDA or ANDA, an amendment or supplement (including any patent certifications or statements), submission of patent information and requests by the NDA holder to amend or withdraw a patent or patent information, submission of a new patent listing dispute, and notification of court actions or written consent to approval) received by FDA on or after the effective date. In addition, a person (including a 505(b)(2) or ANDA applicant) may submit a request under § 314.53(f)(1) for an NDA holder to confirm the accuracy or relevance of previously submitted patent information in light of requirements for submission of patent information on and after the effective date of this final rule.

#### VII. Economic Analysis of Impacts

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all

costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. We believe that this final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because average costs per entity are small, and the regulatory requirement with the highest cost per instance would affect few if any of the smallest entities, we certify that the final rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This final rule would not result in an expenditure in any year that meets or exceeds this amount.

Many provisions of this final rule codify current practice, but some elements will lead to changes that generate additional benefits and costs. Table 2 summarizes the benefits and costs of this final rule. The estimated annualized monetized benefits of this final rule are \$215,247 at a 3 percent or 7 percent discount rate, while the estimated annualized monetized costs are \$266,947



at a 3 percent discount rate and \$275,925 at a 7 percent discount rate. We have also identified, but are unable to quantify, additional impacts from changes to submitted patent information.

Table 2.--Summary of Benefits and Costs

	Benefits	Costs
One-time (Year 1) Cost for Reading the Rule	N/A	\$466,450
Annually Recurring Compliance Costs or Savings (Years 1-10)	\$215,247	\$213,858
Present Value at 3 Percent	\$1,836,098	\$2,277,116
Present Value at 7 Percent	\$1,511,803	\$1,937,983
Annualized Value at 3 Percent	\$215,247	\$266,947
Annualized Value at 7 Percent	\$215,247	\$275,925

The full analysis of economic impacts is available in the docket for this final rule (Ref. 2) and at

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

### VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) and 25.31(a) and (g) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

### IX. Paperwork Reduction Act of 1995

The final rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3520). The title, description, and respondent description of the information collection provisions are shown in the following paragraphs with an estimate of the annual reporting burden. The estimate includes the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Abbreviated New Drug Applications and 505(b)(2) Applications.

Description of Respondents: Respondents to this collection of information are NDA applicants (including 505(b)(2) applicants) and ANDA applicants, patent owners, and their representatives.

Burden Estimate: This final rule implements portions of Title XI of the MMA that pertain to a 505(b)(2) or ANDA applicant's provision of notice of paragraph IV certification to each patent owner and the NDA holder; the availability of 30-month stays of approval on 505(b)(2) applications and ANDAs that are otherwise ready to be approved; submission of amendments and supplements to 505(b)(2) applications and ANDAs; and the types of bioavailability and bioequivalence data that can be used to support these applications. This final rule also amends certain regulations regarding 505(b)(2) applications and ANDAs to facilitate compliance with and efficient enforcement of the FD&C Act.

FDA currently has OMB approval for the collection of information entitled "Application for Food and Drug Administration Approval to Market a New Drug" (OMB control number 0910-0001). This collection of information includes, among other things:

- The requirements in §§ 314.50(i) and 314.94(a)(12) for submission of an appropriate patent certification or statement in a 505(b)(2) application or ANDA;
- the requirements in §§ 314.52 and 314.95 for a 505(b)(2) or ANDA applicant to send notice of any paragraph IV certification to each patent owner and the NDA holder and to amend its 505(b)(2) application or ANDA to certify that notice has been provided and to document receipt of the notice;
- the content requirements in § 314.54 for a 505(b)(2) application;
- the requirements in §§ 314.60 and 314.96 for applicants that amend an unapproved 505(b)(2) application or ANDA, respectively;

- the requirements in §§ 314.70 and 314.97 for supplements submitted to FDA for certain changes to an approved 505(b)(2) application or ANDA;
- the requirements in §§ 314.90 and 314.99 for applicants that request waivers from FDA for compliance with §§ 314.50 through 314.81 or §§ 314.92 through 314.99, respectively;
- the procedures in § 314.107(c) by which a first applicant notifies FDA of the date of first commercial marketing;
- the requirement in § 314.107(e) for an applicant to submit to FDA a copy of certain court decisions related to a patent that is the subject of a paragraph IV certification;
- the requirement in § 314.107(f) for a 505(b)(2) or ANDA applicant to notify FDA immediately of the filing of any legal action within 45 days of receipt of the notice of paragraph IV certification by each patent owner or the NDA holder; and
- the requirement in § 314.107(f) for a patent owner or NDA holder who is an exclusive patent licensee that waives its opportunity to file a legal action for patent infringement within the 45-day period to submit to FDA a waiver in the specified format.

In addition, FDA has OMB approval for the collection of information entitled “General Administrative Procedures: Citizen Petitions; Petition for Reconsideration or Stay of Action; Advisory Opinions” (OMB control number 0910-0191). This collection of information includes, among other things, the requirements in § 314.93 for submitting a suitability petition in accordance with 21 CFR 10.20 and 10.30.

FDA also has OMB approval for the collection of information entitled “Applications for Food and Drug Administration Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed”

(OMB control number 0910-0513). This collection of information includes the requirements in § 314.50(h) for submission of patent information in an NDA, an amendment, or a supplement, as described in § 314.53. Section 314.53 requires that an applicant submitting an NDA, an amendment, or a supplement, except as provided in § 314.53(d)(2), submit on Forms FDA 3542a and 3542 the required patent information described in this section.

Under section 505(b), (c), and (j) of the FD&C Act and this final rule, the following information must be submitted to FDA but is not currently approved by OMB under the PRA.

Section 314.50(i)(1)(i)(C) requires a 505(b)(2) applicant to submit an appropriate patent certification or statement for each patent listed in the Orange Book for one drug product approved in an NDA that is pharmaceutically equivalent to the proposed drug product for which the original 505(b)(2) application is submitted and was approved before the original 505(b)(2) application was submitted. Section 314.54 also describes this requirement. In general, 505(b)(2) applications submitted for a proposed drug product for which there is an approved pharmaceutical equivalent already cite the pharmaceutically equivalent product as a listed drug relied upon to support approval. However, based on our experience reviewing 505(b)(2) applications, we estimate that § 314.50(i)(1)(i)(C) may result in two instances per year in which an applicant is required to identify a pharmaceutically equivalent drug product as a listed drug relied upon and to comply with applicable regulatory requirements (including submission of an appropriate patent certification or statement for each patent listed in the Orange Book for a pharmaceutically equivalent drug product approved in an NDA). Based on an average of 3.4 patents submitted by an NDA holder for listing in the Orange Book, we calculate that the two instances in which a 505(b)(2) applicant is required to identify a pharmaceutically equivalent drug product as a listed drug relied upon will result in 6.8 patent certifications or statements per

year. The burden associated with this requirement in § 314.50(i)(1)(i)(C) is approximately 2 hours per response. In addition, if the patent certification submitted pursuant to § 314.50(i)(1)(i)(C) is a paragraph IV certification, the applicant also must comply with the requirements in § 314.52 for notice of paragraph IV certification.

The burden estimate for sending notice of a paragraph IV certification reflects other changes that reduce the currently approved burden for § 314.52 from 16 hours per response to 15 hours per response, and the additional content requirement in § 314.52(c) that increases the estimated burden by 0.33 hours per response. We are providing an estimate of 15 respondents for § 314.52(a), (b), and (e) to reflect the additional burden that may arise from the requirement in § 314.50(i)(1)(i)(C) if the two 505(b)(2) applicants submit paragraph IV certifications and to update data regarding the estimated number of 505(b)(2) applications that contain one or more paragraph IV certifications, which adds approximately 675 hours (15 hours per response) to the currently approved burden. We separately describe and estimate the burden of the additional content requirement in § 314.52(c).

Sections 314.52(a) and 314.95(a) expand the acceptable delivery methods that may be used to send notice of paragraph IV certification to the NDA holder and each patent owner, and thereby reduce the burden on applicants to submit, under existing § 314.52(a) and (e), a request to FDA to use common alternate delivery methods. We receive approximately 390 written inquiries per year from 505(b)(2) or ANDA applicants requesting permission to send notice of paragraph IV certification by an overnight delivery service. Sections 314.52(a) and 314.95(a) eliminate the requirement to submit a request to use a designated delivery service, as defined in §§ 314.52(g) and 314.95(g). We estimate that approximately 97.5 percent of these written

inquiries will no longer be required because the alternate delivery method would fall within the definition of a “designated delivery service” in §§ 314.52(g) and 314.95(g).

Sections 314.50(i)(6) and 314.94(a)(12)(viii) require a 505(b)(2) or ANDA applicant to amend its patent certification from a paragraph IV certification to a paragraph III certification after the court enters a final decision from which no appeal has been or can be taken, or signs and enters a settlement order or consent decree with a finding of infringement (unless the patent also is found invalid). Sections 314.50(i)(6) and 314.94(a)(12)(viii) also require a 505(b)(2) or ANDA applicant to submit an amended patent certification in certain circumstances after the NDA holder has requested to remove a patent or patent information from the list.

Based on our experience receiving submissions of court decisions or orders with a finding of infringement, and instances in which the patent or patent information has been removed from the list at the request of the NDA holder, we estimate that this requirement may result in approximately 17 and 153 instances per year in which an applicant amends its 505(b)(2) application or ANDA, respectively, to submit a revised patent certification. The burden hours associated with this requirement will be approximately 2 hours per response.

Sections 314.50(i)(6)(iii)(A)(2) and 314.94(a)(12)(viii)(C)(1)(ii) expressly codify the current requirement for a 505(b)(2) or ANDA applicant to submit a patent certification or statement if, after submission of the application, a new patent is issued by the USPTO that in the opinion of the applicant and to the best of its knowledge, claims the listed drug or an approved use for such listed drug and for which information is required to be filed by the NDA holder.

Section 314.95(c) requires that the notice of paragraph IV certification contain a statement that the applicant has received the paragraph IV acknowledgment letter. In addition, § 314.52(c) requires that the notice of paragraph IV certification contain a statement that a

505(b)(2) application that contains any required bioavailability or bioequivalence data has been submitted by the applicant and filed by FDA, as required by section 505(b)(3)(D)(i) of the FD&C Act. We estimate that these additional content requirements for the notice of paragraph IV certification would increase the burden of providing notice of paragraph IV certification by approximately 20 minutes. Based on an estimated average of 20 505(b)(2) applications filed per year that contain one or more paragraph IV certifications (plus the additional burden that may arise from the requirement in § 314.50(i)(1)(i)(C) if the 2 505(b)(2) applicants submit paragraph IV certifications) and 400 ANDAs received per year that contain one or more paragraph IV certifications, we estimate that there will be 60 and 1,200 responses per year, respectively, and the burden hours associated with this requirement will be approximately 20 minutes per response.

Sections 314.52(d)(1) and 314.95(d)(1) require notice of paragraph IV certification regardless of whether notice has already been provided for another paragraph IV certification contained in the 505(b)(2) application or ANDA or an amendment or supplement to the 505(b)(2) application or ANDA, as required by section 505(b)(3)(B)(ii) and (j)(2)(B)(ii)(II) of the FD&C Act. Since enactment of the MMA in 2003, FDA has regulated directly from the statute and required notice of paragraph IV certification in these circumstances, and the burden associated with this statutory requirement is currently approved under OMB control number 0910-0001.

Sections 314.52(e) and 314.95(e) would permit a 505(b)(2) or ANDA applicant to submit a single amendment containing documentation of timely sending and receipt of notice of paragraph IV certification. Currently, an applicant is required to amend its 505(b)(2) application or ANDA both at the time of sending notice of paragraph IV certification and after the notice

was received by each patent owner and the NDA holder (see existing §§ 314.52(b) and (e) and 314.95(b) and (e)). Section 314.95(e) also requires an ANDA applicant to include in its amendment a dated printout of the Orange Book entry for the RLD. The burden associated with this statutory requirement is currently approved under OMB control number 0910-0001.

Section 314.53(c)(2) decreases the patent information that NDA applicants are currently required to submit for listing in the Orange Book. Section 314.53(c)(2) requires submission of patent information on whether a drug substance patent claims a polymorph only if such patent claims only a polymorph that is the same active ingredient described in the NDA or supplement. Section 314.53(c)(2) also provides that an applicant that submits information for a patent that claims either the drug substance or drug product and meets the requirements for patent listing on that basis is not required to provide information on whether that patent also claims the drug product or drug substance, respectively. Section 314.53(c)(2) also modifies requirements for submission of patent information on method-of-use patents. The information collection resulting from existing § 314.50(h) (citing § 314.53) and Form FDA 3542a has been approved by OMB under control number 0910-0513 for FDA's estimate of 20 hours per response. We previously estimated that the burden of Form FDA 3542a would fall by 3 hours per response. We now estimate that the burden for Form FDA 3542a will be reduced by 5 hours from 20 hours to 15 hours per response; we further estimate that the burden for Form FDA 3542 will increase by 5 hours from 5 to 10 hours per response. We have shifted a portion of the time spent preparing Form FDA 3542a to the estimated time preparing Form FDA 3542 to reflect the additional time spent by the NDA holder to develop the use code in accordance with FDA's revised regulations and identify the specific section(s) and subsection(s) of labeling that describe the specific approved method of use claimed by the patent.



Section 314.53(d)(2) avoids duplicative submission of patent information that would accompany supplements to NDAs and requires such information only for a supplement to add or change the dosage form or route of administration, to add or change the strength, to change the drug product from prescription to OTC use, or to revise previously submitted patent information that differently or no longer claims the changed product.

Section 314.53(f)(1) provides a more detailed description of the procedure for patent listing disputes directed to the accuracy or relevance of submitted patent information, and establishes additional requirements for patent listing disputes directed to method-of-use claims. Based on our experience, we estimate that there may be approximately 12 instances per year in which a person submits a patent listing dispute, and a corresponding 12 instances per year in which the NDA holder is required to respond to the patent listing dispute. In light of the additional requirements for patent listing disputes directed to method-of-use claims, we estimate that the burden associated with § 314.53(f)(1) will be approximately 10 hours per response.

Section 314.53(f)(2) expressly requires correction or change of patent information if the NDA holder determines that a patent or patent claim no longer meets the statutory requirements for listing, if the NDA holder is required by court order to amend patent information or withdraw a patent from the list, or if the term of a listed patent is extended under 35 U.S.C. 156(e). We estimate that these corrections and changes of patent information would result in approximately 39 submissions of Form FDA 3542 or other written submission, as provided in § 314.53(f)(2), by approximately 27 NDA holders. We further estimate that the burden hours associated with the requirement in § 314.53(f)(2) would be approximately 1 hour per response.

Section 505(b)(4)(A) and (j)(2)(D)(i) of the FD&C Act generally prohibits the submission of certain types of changes in an amendment or a supplement to a 505(b)(2)

application or an ANDA, respectively. Sections 314.60(e) and 314.70(h) would prohibit an applicant from amending or supplementing a 505(b)(2) application to seek approval of a drug that has been modified to have a different active ingredient, different route of administration, different dosage form, or certain differences in excipients than the drug proposed in the original submission of the 505(b)(2) application. These changes must be requested in a new 505(b)(2) application. This final requirement conforms with FDA's current policy regarding the types of proposed changes to a drug product that should be submitted as a separate application (see guidance for industry on "Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees" (December 2004), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>). Accordingly, the burden associated with this statutory requirement is currently approved under OMB control number 0910-0001.

Sections 314.60(f) and 314.96(d) require an applicant to submit a patent certification if approval is sought for the following types of amendments to a 505(b)(2) application or ANDA: (1) To add a new indication or other condition of use; (2) to add a new strength; (3) to make other than minor changes in product formulation; or (4) to change the physical form or crystalline structure of the active ingredient. Although currently the submission of a patent certification is required if, at any time before approval, the applicant learns that the previously submitted patent certification is no longer accurate with respect to the pending application or supplement, as amended, the patent certification requirements would be broadened under this regulation. We estimate that this broadened requirement may result in approximately six instances per year in which an applicant is required to submit a patent certification with an amendment to its 505(b)(2) application. We further estimate that this requirement may result in

approximately 100 instances per year in which an applicant is required to submit a patent certification with an amendment to its ANDA. The burden hours associated with these requirements are estimated to be approximately 2 hours per response.

Sections 314.96(c) and 314.97(b) prohibit an ANDA applicant from amending or supplementing an ANDA to seek approval of a drug referring to a listed drug that is different from the RLD identified in the ANDA. An applicant must submit a change of the RLD in a new ANDA. We estimate that approximately one ANDA applicant per year will be required to submit a new ANDA instead of submitting an amendment for a change of the RLD. We also estimate that approximately one ANDA applicant per year will be required to submit a new ANDA instead of submitting a supplement for a change of the RLD. We further estimate that the burden of submitting an ANDA and complying with applicable regulatory requirements, including any required study to demonstrate bioequivalence to the new RLD, will be approximately 300 hours for each of the estimated two responses per year.

Section 314.107(e) expands the scope of the court actions and written consent to approval related to a patent described in § 314.107(b)(3) that are required to be submitted to FDA. Section 314.107(e) also requires submission of any court order pursuant to 35 U.S.C. 271(e)(4)(A) ordering that a 505(b)(2) application or ANDA may be approved no earlier than the date specified. Based on our experience, we estimate that 247 505(b)(2) and ANDA applicants will be required to submit a copy of a court action, written consent to approval, or written notification of appeal in approximately 494 instances per year. We continue to estimate that the burden associated with submitting a copy of these documents to FDA (as approved in OMB control number 0910-0001) is approximately 30 minutes per response.

The estimated burden of this collection of information is described in Table 3.

Table 3--Estimated Annual Reporting Burden<sup>1</sup>

21 CFR section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Average Burden per Response (in Hours)	Total Hours
314.50(i)(1)	2	3.4	6.8	2	14
314.50(i)(6)	17	1	17	2	34
314.52(a), (b), and (e)	15	3	45	15	675
314.52(c)	22	3	66	0.33 (20 minutes)	22
314.53(f)(1)	24	1	24	10	240
314.53(f)(2)	27	1.4	39	1	39
314.60(f)	6	1	6	2	12
314.94(a)(12)(viii)	153	1	153	2	306
314.95(c)	400	3	1,200	0.33 (20 minutes)	400
314.96(c)	1	1	1	300	300
314.96(d)	100	1	100	2	200
314.97(b)	1	1	1	300	300
314.107(e)	247	2	494	0.5 (30 minutes)	247
Total Reporting Burden Hours					2,789

<sup>1</sup> There are no capital costs or operating and maintenance costs associated with this collection of information.

The information collection provisions in this final rule have been submitted to OMB for review as required by section 3507(d) of the Paperwork Reduction Act of 1995.

Before the effective date of this final rule, FDA will publish a notice in the Federal Register announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

## X. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. We have determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism

implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

## XI. References

The following references are on display in the Division of Dockets Management (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <http://www.regulations.gov>. FDA has verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. Federal Trade Commission, Report on “Generic Drug Entry Prior to Patent Expiration: An FTC Study” (July 2002), available at [http://www.ftc.gov/sites/default/files/documents/reports/generic-drug-entry-prior-patent-expiration-ftc-study/genericdrugstudy\\_0.pdf](http://www.ftc.gov/sites/default/files/documents/reports/generic-drug-entry-prior-patent-expiration-ftc-study/genericdrugstudy_0.pdf).

2. Final Regulatory Impact Analysis, Final Regulatory Flexibility Analysis, and Unfunded Mandates Reform Act Analysis for Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, available at <http://www.fda.gov/aboutfda/reportsmanualsforms/reports/economicanalyses/default.htm>.

## List of Subjects

### 21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

### 21 CFR Part 320

Drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 314 and 320 are amended as follows:

**PART 314--APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG**

1. The authority citation for part 314 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 355f, 356, 356a, 356b, 356c, 356e, 360cc, 371, 374, 379e, 379k-1.

2. Section 314.3 is revised to read as follows:

§ 314.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the Federal Food, Drug, and Cosmetic Act apply to those terms when used in this part and part 320 of this chapter.

- (b) The following definitions of terms apply to this part and part 320 of this chapter:

180-day exclusivity period is the 180-day period beginning on the date of the first commercial marketing of the drug (including the commercial marketing of the reference listed drug) by any first applicant. The 180-day period ends on the day before the date on which an ANDA submitted by an applicant other than a first applicant could be approved.

505(b)(2) application is an NDA submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for a drug for which at least some of the investigations described in section 505(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act and relied upon by the applicant for approval of the NDA were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

Abbreviated application, abbreviated new drug application, or ANDA is the application described under § 314.94, including all amendments and supplements to the application.

Acknowledgment letter is a written, postmarked communication from FDA to an applicant stating that the Agency has determined that an ANDA is sufficiently complete to permit a substantive review. An acknowledgment letter indicates that the ANDA is regarded as received.

Act is the Federal Food, Drug, and Cosmetic Act (section 201 et seq. (21 U.S.C. 301 et seq.)).

Active ingredient is any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

Active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

ANDA holder is the applicant that owns an approved ANDA.

Applicant is any person who submits an NDA (including a 505(b)(2) application) or ANDA or an amendment or supplement to an NDA or ANDA under this part to obtain FDA approval of a new drug and any person who owns an approved NDA (including a 505(b)(2) application) or ANDA.

Application, new drug application, or NDA is the application described under § 314.50, including all amendments and supplements to the application. An NDA refers to “stand-alone” applications submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and to 505(b)(2) applications.

Approval letter is a written communication to an applicant from FDA approving an NDA or an ANDA.

Assess the effects of the change is to evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

Authorized generic drug is a listed drug, as defined in this section, that has been approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act and is marketed, sold, or distributed directly or indirectly to the retail class of trade with labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trademark that differs from that of the listed drug.

Bioavailability is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action.

Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar



dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended-release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. For drug products that are not intended to be absorbed into the bloodstream, bioequivalence may be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action.

Bioequivalence requirement is a requirement imposed by FDA for in vitro and/or in vivo testing of specified drug products that must be satisfied as a condition of marketing.

Class 1 resubmission is the resubmission of an NDA or efficacy supplement, following receipt of a complete response letter, that contains one or more of the following: Final printed labeling, draft labeling, certain safety updates, stability updates to support provisional or final dating periods, commitments to perform postmarketing studies (including proposals for such studies), assay validation data, final release testing on the last lots used to support approval, minor reanalyses of previously submitted data, and other comparatively minor information.

Class 2 resubmission is the resubmission of an NDA or efficacy supplement, following receipt of a complete response letter, that includes any item not specified in the definition of “Class 1 resubmission,” including any item that would require presentation to an advisory committee.

Commercial marketing is the introduction or delivery for introduction into interstate commerce of a drug product described in an ANDA, outside the control of the ANDA applicant, except that the term does not include transfer of the drug product for investigational use under part 312 of this chapter or transfer of the drug product to parties identified in the ANDA for reasons other than sale. Commercial marketing includes the introduction or delivery for introduction into interstate commerce of the reference listed drug by the ANDA applicant.

Complete response letter is a written communication to an applicant from FDA usually describing all of the deficiencies that the Agency has identified in an NDA or ANDA that must be satisfactorily addressed before it can be approved.

Component is any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

Date of approval is the date on the approval letter from FDA stating that the NDA or ANDA is approved, except that the date of approval for an NDA described in section 505(x)(1) of the Federal Food, Drug, and Cosmetic Act is determined as described in section 505(x)(2) of the Federal Food, Drug, and Cosmetic Act. “Date of approval” refers only to a final approval and not to a tentative approval.

Dosage form is the physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product. This includes such factors as:

- (1) The physical appearance of the drug product;
- (2) The physical form of the drug product prior to dispensing to the patient;
- (3) The way the product is administered; and
- (4) The design features that affect frequency of dosing.

Drug product is a finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

Drug substance is an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient.

Efficacy supplement is a supplement to an approved NDA proposing to make one or more related changes from among the following changes to product labeling:

- (1) Add or modify an indication or claim;
- (2) Revise the dose or dose regimen;
- (3) Provide for a new route of administration;
- (4) Make a comparative efficacy claim naming another drug product;
- (5) Significantly alter the intended patient population;
- (6) Change the marketing status from prescription to over-the-counter use;
- (7) Provide for, or provide evidence of effectiveness necessary for, the traditional approval of a product originally approved under subpart H of this part; or
- (8) Incorporate other information based on at least one adequate and well-controlled clinical study.

FDA or Agency is the Food and Drug Administration.

First applicant is an ANDA applicant that, on the first day on which a substantially complete application containing a paragraph IV certification is submitted for approval of a drug, submits a substantially complete application that contains, and for which the applicant lawfully maintains, a paragraph IV certification for the drug.

Inactive ingredient is any component other than an active ingredient.

Listed drug is a new drug product that has been approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act for safety and effectiveness or under section 505(j) of the Federal Food, Drug, and Cosmetic Act, which has not been withdrawn or suspended under section 505(e)(1) through (5) or section 505(j)(6) of the Federal Food, Drug, and Cosmetic Act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification in the current edition of FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (the list) as an approved drug. A drug product is deemed to be a listed drug on the date of approval for the NDA or ANDA for that drug product.

NDA holder is the applicant that owns an approved NDA.

Newly acquired information is data, analyses, or other information not previously submitted to the Agency, which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.

Original application or original NDA is a pending NDA for which FDA has never issued a complete response letter or approval letter, or an NDA that was submitted again after FDA had refused to file it or after it was withdrawn without being approved.

Paragraph IV acknowledgment letter is a written, postmarked communication from FDA to an applicant stating that the Agency has determined that a 505(b)(2) application or ANDA containing a paragraph IV certification is sufficiently complete to permit a substantive review. A

paragraph IV acknowledgment letter indicates that the 505(b)(2) application is regarded as filed or the ANDA is regarded as received.

Paragraph IV certification is a patent certification of invalidity, unenforceability, or noninfringement described in § 314.50(i)(1)(i)(A)(4) or § 314.94(a)(12)(i)(A)(4).

Patent owner is the owner of the patent for which information is submitted for an NDA.

Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

Postmark is an independently verifiable evidentiary record of the date on which a document is transmitted, in an unmodifiable format, to another party. For postmarks made by the U.S. Postal Service or a designated delivery service, the date of transmission is the date on which the document is received by the domestic mail service of the U.S. Postal Service or by a designated delivery service. For postmarks documenting an electronic event, the date of

transmission is the date (in a particular time zone) that FDA sends the electronic transmission on its host system as evidenced by a verifiable record. If the sender and the intended recipient are located in different time zones, it is the sender's time zone that provides the controlling date of electronic transmission.

Reference listed drug is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.

Reference standard is the drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an in vivo bioequivalence study required for approval.

Resubmission, in the context of a complete response letter, is submission by the applicant of all materials needed to fully address all deficiencies identified in the complete response letter. An NDA or ANDA for which FDA issued a complete response letter, but which was withdrawn before approval and later submitted again, is not a resubmission.

Right of reference or use is the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an NDA, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary.

Same drug product formulation is the formulation of the drug product submitted for approval and any formulations that have minor differences in composition or method of manufacture from the formulation submitted for approval, but are similar enough to be relevant to the Agency's determination of bioequivalence.

Specification is the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved NDA or ANDA to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container

closure systems, and other materials used in the production of a drug substance or drug product. For the purpose of this definition, acceptance criteria means numerical limits, ranges, or other criteria for the tests described.

Strength is the amount of drug substance contained in, delivered, or deliverable from a drug product, which includes:

(1)(i) The total quantity of drug substance in mass or units of activity in a dosage unit or container closure (e.g., weight/unit dose, weight/volume or weight/weight in a container closure, or units/volume or units/weight in a container closure); and/or, as applicable.

(ii) The concentration of the drug substance in mass or units of activity per unit volume or mass (e.g., weight/weight, weight/volume, or units/volume); or

(2) Such other criteria the Agency establishes for determining the amount of drug substance contained in, delivered, or deliverable from a drug product if the weights and measures described in paragraph (i) of this definition do not apply (e.g., certain drug-device combination products for which the amount of drug substance is emitted per use or unit time).

Substantially complete application is an ANDA that on its face is sufficiently complete to permit a substantive review. Sufficiently complete means that the ANDA contains all the information required under section 505(j)(2)(A) of the Federal Food, Drug, and Cosmetic Act and does not contain a deficiency described in § 314.101(d) and (e).

Tentative approval is notification that an NDA or ANDA otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act, but cannot be approved because there is a 7-year period of orphan exclusivity for a listed drug under section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter, or that a 505(b)(2) application or ANDA otherwise meets the requirements for approval under the Federal

Food, Drug, and Cosmetic Act, but cannot be approved until the conditions in § 314.107(b)(1)(iii), (b)(3), or (c) are met; because there is a period of exclusivity for the listed drug under § 314.108; because there is a period of pediatric exclusivity for the listed drug under section 505A of the Federal Food, Drug, and Cosmetic Act; because there is a period of exclusivity for the listed drug under section 505E of the Federal Food, Drug, and Cosmetic Act; or because a court order pursuant to 35 U.S.C. 271(e)(4)(A) orders that the NDA or ANDA may be approved no earlier than the date specified. A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval letter after any necessary additional review of the NDA or ANDA.

The list is the list of approved drug products published in FDA's current "Approved Drug Products With Therapeutic Equivalence Evaluations," available electronically on FDA's Web site at <http://www.fda.gov/cder>.

Therapeutic equivalents are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

3. Amend § 314.50 as follows:

a. Remove the word "shall" and add in its place the word "must" wherever it appears in paragraphs (a) introductory text, (a)(5), (d)(1)(v), (d)(5)(v), (d)(5)(vi)(a) and (b), (e)(2) introductory text, (f)(3), (g)(2), and (k);

b. Remove the word "application" and add in its place "NDA" wherever it appears in paragraphs (a)(5), (b), (c)(1), (c)(2)(i), (c)(2)(iv) through (viii), (d) introductory text, (d)(1)(i), (d)(1)(ii)(a), (d)(1)(iii) through (v), (d)(3)(ii), (d)(5)(iv), (d)(5)(vi)(b), (e)(1)(i) introductory text,



(e)(2) introductory text, (f) introductory text, (f)(1) through (3), (g)(2), (h), (j)(4) introductory text, (j)(4)(i) and (ii), (k), (l) heading, (l)(1) introductory text, and (l)(4);

c. Remove the word “act” and add in its place “Federal Food, Drug, and Cosmetic Act” in paragraphs (d) introductory text, (d)(5)(vi)(b), and (j)(3);

d. Remove the phrase “Prior to the submission of” and add in its place the words “Before submitting” and remove the phrase “are required to” and add in its place the word “must” wherever it appears in paragraph (d)(5)(vi)(b);

e. Remove the word “shall” and add in its place the word “must” and remove the phrase “new drug application” and add in its place “NDA” in paragraph (j) introductory text; and

f. Revise the section heading, introductory text, and paragraphs (a)(1), (e)(1) introductory text, (f)(4), (g)(3), (i), the first two sentences of paragraph (j)(4)(iii), and (l)(2) and (3).

The revisions read as follows:

§ 314.50 Content and format of an NDA.

NDAAs and supplements to approved NDAs are required to be submitted in the form and contain the information, as appropriate for the particular submission, required under this section. Three copies of the NDA are required: An archival copy, a review copy, and a field copy. An NDA for a new chemical entity will generally contain an application form, an index, a summary, five or six technical sections, case report tabulations of patient data, case report forms, drug samples, and labeling, including, if applicable, any Medication Guide required under part 208 of this chapter. Other NDAs will generally contain only some of those items, and information will be limited to that needed to support the particular submission. These include an NDA of the type described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, an amendment, and

a supplement. The NDA is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source. FDA will maintain guidance documents on the format and content of NDAs to assist applicants in their preparation.

(a) \* \* \*

(1) The name and address of the applicant; the date of the NDA; the NDA number if previously issued (for example, if the NDA is a resubmission or an amendment or supplement); the name of the drug product, including its established, proprietary, code, and chemical names; the dosage form and strength; the route of administration; the identification numbers of all INDs (as defined in § 312.3(b) of this chapter) that are referenced in the NDA; the identification numbers of all drug master files and other applications under this part that are referenced in the NDA; and the drug product's proposed indications for use.

\* \* \* \* \*

(e) \* \* \* (1) Upon request from FDA, the applicant must submit the samples described below to the places identified in the Agency's request. FDA generally will ask applicants to submit samples directly to two or more Agency laboratories that will perform all necessary tests on the samples and validate the applicant's analytical procedures.

\* \* \* \* \*

(f) \* \* \*

(4) Presentation and format. Applicants are invited to meet with FDA before submitting an NDA to discuss the presentation and format of supporting information. If the applicant and

FDA agree, the applicant may submit tabulations of patient data and case report forms in an alternate form.

(g) \* \* \*

(3) If an applicant who submits an NDA under section 505(b) of the Federal Food, Drug, and Cosmetic Act obtains a “right of reference or use,” as defined under § 314.3(b), to an investigation described in clause (A) of section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, the applicant must include in its NDA a written statement signed by the owner of the data from each such investigation that the applicant may rely on in support of the approval of its NDA, and provide FDA access to, the underlying raw data that provide the basis for the report of the investigation submitted in its NDA.

\* \* \* \* \*

(i) Patent certification--(1) Contents. A 505(b)(2) application is required to contain the following:

(i) Patents claiming drug substance, drug product, or method of use. (A) An appropriate patent certification or statement with respect to each patent issued by the U.S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the drug substance or drug product on which investigations that are relied upon by the applicant for approval of its 505(b)(2) application were conducted or that claims an approved use for such drug and for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53. For each such patent, the applicant must provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

(1) That the patent information has not been submitted to FDA. The applicant must entitle such a certification “Paragraph I Certification”;

(2) That the patent has expired. The applicant must entitle such a certification “Paragraph II Certification”;

(3) The date on which the patent will expire. The applicant must entitle such a certification “Paragraph III Certification”; or

(4)(i) That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the 505(b)(2) application is submitted. The applicant must entitle such a certification “Paragraph IV Certification”. This certification must be submitted in the following form:

I, (name of applicant), certify that Patent No. \_\_\_\_\_ (is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of) (name of proposed drug product) for which this 505(b)(2) application is submitted.

(ii) The certification must be accompanied by a statement that the applicant will comply with the requirements under § 314.52(a) with respect to providing a notice to each owner of the patent or its representative and to the NDA holder (or, if the NDA holder does not reside or maintain a place of business within the United States, its attorney, agent, or other authorized official) for the drug product that is claimed by the patent or a use of which is claimed by the patent and with the requirements under § 314.52(b) with respect to sending the notice and under § 314.52(c) with respect to the content of the notice.

(B) If the drug on which investigations that are relied upon by the applicant were conducted is itself a licensed generic drug of a patented drug first approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act, an appropriate patent certification or statement

under this section with respect to each patent that claims the first-approved patented drug or that claims an approved use for such a drug.

(C) If, before the date of submission of an original 505(b)(2) application, there is a drug product approved in an NDA that is pharmaceutically equivalent to the drug product for which the original 505(b)(2) application is submitted, an appropriate patent certification or statement under this section with respect to each patent that claims the drug substance or drug product or that claims an approved use for one such drug product.

(ii) No relevant patents. If, in the opinion of the applicant and to the best of its knowledge, there are no patents described in paragraph (i)(1)(i) of this section, a certification in the following form:

In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the drug or drugs on which investigations that are relied upon in this 505(b)(2) application were conducted or that claim a use of such drug or drugs.

(iii) Method-of-use patent. (A) If information that is submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53 is for a method-of-use patent, and the labeling for the drug product for which the applicant is seeking approval does not include an indication or other condition of use that is covered by the method-of-use patent, a statement explaining that the method-of-use patent does not claim a proposed indication or other condition of use.

(B) If the labeling of the drug product for which the applicant is seeking approval includes an indication or other condition of use that, according to the patent information submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53 or in the opinion of the applicant, is claimed by a method-of-use patent, the applicant must submit an applicable certification under paragraph (i)(1)(i) of this section.

(2) [Reserved]

(3) Licensing agreements. If a 505(b)(2) application is submitted for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, the applicant must submit a paragraph IV certification as to that patent and a statement that the applicant has been granted a patent license. If the patent owner consents to approval of the 505(b)(2) application (if otherwise eligible for approval) as of a specific date, the 505(b)(2) application must contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to approval of the 505(b)(2) application as of a specific date.

(4) Untimely filing of patent information. (i) If a patent described in paragraph (i)(1)(i)(A) of this section is issued and the holder of the approved NDA for the patented drug does not file with FDA the required information on the patent within 30 days of issuance of the patent, an applicant who submitted a 505(b)(2) application that, before the submission of the patent information, contained an appropriate patent certification or statement is not required to submit a patent certification or statement to address the patent or patent information that is late-listed with respect to the pending 505(b)(2) application. Except as provided in § 314.53(f)(1), an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will be considered untimely filing of patent information unless:

(A) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of patent issuance;

(B) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of approval of a corresponding change to product labeling; or

(C) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of a decision by the U.S. Patent and Trademark Office or by a Federal district court, the Court of Appeals for the Federal Circuit, or the U.S. Supreme Court that is specific to the patent and alters the construction of a method-of-use claim(s) of the patent, and the amendment contains a copy of the decision.

(ii) An applicant whose 505(b)(2) application is submitted after the NDA holder's untimely filing of patent information or whose 505(b)(2) application was previously filed but did not contain an appropriate patent certification or statement at the time of the patent submission must submit a certification under paragraph (i)(1)(i) of this section and/or a statement under paragraph (i)(1)(iii) of this section as to that patent.

(5) Disputed patent information. If an applicant disputes the accuracy or relevance of patent information submitted to FDA, the applicant may seek a confirmation of the correctness of the patent information in accordance with the procedures under § 314.53(f). Unless the patent information is withdrawn, the applicant must submit an appropriate certification or statement for each listed patent.

(6) Amended certifications. A patent certification or statement submitted under paragraphs (i)(1)(i) through (iii) of this section may be amended at any time before the approval of the 505(b)(2) application. An applicant must submit an amended certification as an amendment to a pending 505(b)(2) application. If an applicant with a pending 505(b)(2) application voluntarily makes a patent certification for an untimely filed patent, the applicant may withdraw the patent certification for the untimely filed patent. Once an amendment is submitted to change the certification, the 505(b)(2) application will no longer be considered to contain the prior certification.

(i) After finding of infringement. An applicant who has submitted a paragraph IV certification and is sued for patent infringement must submit an amendment to change its certification if a court enters a final decision from which no appeal has been or can be taken, or signs and enters a settlement order or consent decree in the action that includes a finding that the patent is infringed, unless the final decision, settlement order, or consent decree also finds the patent to be invalid. In its amendment, the applicant must certify under paragraph (i)(1)(i)(A)(3) of this section that the patent will expire on a specific date or, with respect to a patent claiming a method of use, the applicant may instead provide a statement under paragraph (i)(1)(iii) of this section if the applicant amends its 505(b)(2) application such that the applicant is no longer seeking approval for a method of use claimed by the patent. Once an amendment for the change has been submitted, the 505(b)(2) application will no longer be considered to contain a paragraph IV certification to the patent. If a final decision finds the patent to be invalid and infringed, an amended certification is not required.

(ii) After request to remove a patent or patent information from the list. If the list reflects that an NDA holder has requested that a patent or patent information be removed from the list and no ANDA applicant is eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent or patent information will be removed and any applicant with a pending 505(b)(2) application (including a tentatively approved 505(b)(2) application) who has made a certification with respect to such patent must submit an amendment to withdraw its certification. In the amendment, the applicant must state the reason for withdrawing the certification or statement (that the patent has been removed from the list). If the list reflects that an NDA holder has requested that a patent or patent information be removed from the list and one or more first applicants are eligible for 180-day exclusivity based on a paragraph IV certification to that



patent, the patent will remain listed until any 180-day exclusivity based on that patent has expired or has been extinguished. A 505(b)(2) applicant is not required to provide or maintain a certification to a patent or patent information that remains listed only for purposes of a first applicant's 180-day exclusivity for its ANDA. Once an amendment to withdraw the certification has been submitted, the 505(b)(2) application will no longer be considered to contain a paragraph IV certification to the patent. If removal of a patent from the list results in there being no patents listed for the listed drug(s) identified in the 505(b)(2) application, the applicant must submit an amended certification reflecting that there are no listed patents.

(iii) Other amendments. (A) Except as provided in paragraphs (i)(4) and (i)(6)(iii)(B) of this section:

(1) An applicant must amend a submitted certification or statement if, at any time before the approval of the 505(b)(2) application, the applicant learns that the submitted certification or statement is no longer accurate; and

(2) An applicant must submit an appropriate patent certification or statement under paragraph (i)(1) of this section if, after submission of the 505(b)(2) application, a new patent is issued by the U.S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims a listed drug relied upon or that claims an approved use for such listed drug for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53.

(B) An applicant is not required to submit a supplement to change a submitted certification when information on an otherwise applicable patent is submitted after the approval of the 505(b)(2) application.

(j) \* \* \*

(4) \* \* \*

(iii) \* \* \* If the applicant was the sponsor named in the Form FDA 1571 for an IND under which the new clinical investigation(s) that is essential to the approval of its NDA was conducted, identification of the IND by number. If the applicant was not the sponsor of the IND under which the clinical investigation(s) was conducted, a certification that the applicant or its predecessor in interest provided substantial support for the clinical investigation(s) that is essential to the approval of its NDA, and information supporting the certification. \* \* \*

\* \* \* \* \*

(1) \* \* \*

(2) Review copy. The applicant must submit a review copy of the NDA. Each of the technical sections, described in paragraphs (d)(1) through (6) of this section, in the review copy is required to be separately bound with a copy of the application form required under paragraph (a) of this section and a copy of the summary required under paragraph (c) of this section.

(3) Field copy. The applicant must submit a field copy of the NDA that contains the technical section described in paragraph (d)(1) of this section, a copy of the application form required under paragraph (a) of this section, a copy of the summary required under paragraph (c) of this section, and a certification that the field copy is a true copy of the technical section described in paragraph (d)(1) of this section contained in the archival and review copies of the NDA.

\* \* \* \* \*

4. Section 314.52 is revised to read as follows:

§ 314.52 Notice of certification of invalidity, unenforceability, or noninfringement of a patent.

(a) Notice of certification. For each patent that claims the listed drug or drugs relied upon or that claims a use for such listed drug or drugs and for which the 505(b)(2) applicant submits a paragraph IV certification, the applicant must send notice of such certification by registered or certified mail, return receipt requested, or by a designated delivery service, as defined in paragraph (g) of this section, to each of the following persons:

(1) Each owner of the patent that is the subject of the certification or the representative designated by the owner to receive the notice. The name and address of the patent owner or its representative may be obtained from the U.S. Patent and Trademark Office; and

(2) The holder of the approved NDA under section 505(b) of the Federal Food, Drug, and Cosmetic Act for each drug product which is claimed by the patent or a use of which is claimed by the patent and for which the applicant is seeking approval, or, if the NDA holder does not reside or maintain a place of business within the United States, the NDA holder's attorney, agent, or other authorized official. The name and address of the NDA holder or its attorney, agent, or authorized official may be obtained by sending a written or electronic communication to the Orange Book Staff, Office of Generic Drugs, 7620 Standish Pl., Rockville, MD 20855, or to the Orange Book Staff at the email address listed on the Agency's Web site at <http://www.fda.gov>.

(3) This paragraph (a) does not apply to a method-of-use patent that does not claim a use for which the applicant is seeking approval.

(4) An applicant may send notice by an alternative method only if FDA has agreed in advance that the method will produce an acceptable form of documentation.

(b) Sending the notice. (1) Except as provided under paragraph (d) of this section, the applicant must send the notice required by paragraph (a) of this section on or after the date of filing described in § 314.101(a)(2) or (3), as applicable, but not later than 20 days after the date

of the postmark on the paragraph IV acknowledgment letter. The 20-day clock described in this paragraph (b) begins on the day after the date of the postmark on the paragraph IV acknowledgment letter. When the 20th day falls on Saturday, Sunday, or a Federal holiday, the 20th day will be the next day that is not a Saturday, Sunday, or Federal holiday.

(2) Any notice required by paragraph (a) of this section is invalid if it is sent before the date of filing described in § 314.101(a)(2) or, if FDA notifies the applicant that FDA has refused to file the 505(b)(2) application, before the date described in § 314.101(a)(3) on which the 505(b)(2) application is filed. The applicant will not have complied with this paragraph (b) until it sends valid notice.

(3) The applicant must submit to FDA an amendment to its 505(b)(2) application that includes a statement certifying that the notice has been provided to each person identified under paragraph (a) of this section and that the notice met the content requirement under paragraph (c) of this section. A copy of the notice itself need not be submitted to the Agency.

(c) Content of a notice. In the notice, the applicant must cite section 505(b)(3)(D) of the Federal Food, Drug, and Cosmetic Act and the notice must include, but is not limited to, the following information:

(1) A statement that a 505(b)(2) application that contains any required bioavailability or bioequivalence studies has been submitted by the applicant and filed by FDA.

(2) The NDA number.

(3) The established name, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act, of the proposed drug product.

(4) The active ingredient, strength, and dosage form of the proposed drug product.

(5) The patent number and expiration date of each patent on the list alleged to be invalid, unenforceable, or not infringed.

(6) A detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed. The applicant must include in the detailed statement:

(i) For each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed.

(ii) For each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation.

(7) If the applicant alleges that the patent will not be infringed and the applicant seeks to preserve the option to later file a civil action for declaratory judgment in accordance with section 505(c)(3)(D) of the Federal Food, Drug, and Cosmetic Act, then the notice must be accompanied by an offer of confidential access to the 505(b)(2) application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the paragraph IV certification.

(8) If the applicant does not reside or have a place of business in the United States, the name and address of an agent in the United States authorized to accept service of process for the applicant.

(d) Amendment or supplement to a 505(b)(2) application. (1) If, after the date of filing described in § 314.101(a)(2) or (3), as applicable, an applicant submits an amendment or supplement to its 505(b)(2) application that includes a paragraph IV certification, the applicant must send the notice required by paragraph (a) of this section at the same time that the amendment or supplement to the 505(b)(2) application is submitted to FDA, regardless of

whether the applicant has already given notice with respect to another such certification contained in the 505(b)(2) application or in an amendment or supplement to the 505(b)(2) application.

(2) If, before the date of filing described in § 314.101(a)(2) or (3), as applicable, an applicant submits a paragraph IV certification in an amendment, the applicant must send the notice required by paragraph (a) of this section in accordance with the procedures in paragraph (b) of this section.

(3) An applicant that submits an amendment or supplement to seek approval of a different strength must provide notice of any paragraph IV certification in accordance with paragraph (d)(1) or (2) of this section, as applicable.

(e) Documentation of timely sending and receipt of notice. The applicant must amend its 505(b)(2) application to provide documentation of the date of receipt of the notice required under paragraph (a) of this section by each person provided the notice. The amendment must be submitted to FDA within 30 days after the last date on which notice was received by a person described in paragraph (a) of this section. The applicant's amendment also must include documentation that its notice was sent on a date that complies with the timeframe required by paragraph (b) or (d) of this section, as applicable. FDA will accept, as adequate documentation of the date the notice was sent, a copy of the registered mail receipt, certified mail receipt, or receipt from a designated delivery service, as defined in paragraph (g) of this section. FDA will accept as adequate documentation of the date of receipt a return receipt, a signature proof of delivery by a designated delivery service, or a letter acknowledging receipt by the person provided the notice. An applicant may rely on another form of documentation only if FDA has

agreed to such documentation in advance. A copy of the notice itself need not be submitted to the Agency.

(f) Forty-five day period after receipt of notice. If the requirements of this section are met, the Agency will presume the notice to be complete and sufficient and will count the day following the date of receipt of the notice by the patent owner or its representative and by the approved NDA holder or its attorney, agent, or other authorized official as the first day of the 45-day period provided for in section 505(c)(3)(C) of the Federal Food, Drug, and Cosmetic Act. FDA may, if the applicant amends its 505(b)(2) application with a written statement that a later date should be used, count from such later date.

(g) Designated delivery services. (1) For purposes of this section, the term “designated delivery service” is any delivery service provided by a trade or business that the Agency determines:

- (i) Is available to the general public throughout the United States;
- (ii) Records electronically to its database, kept in the regular course of its business, or marks on the cover in which any item referred to in this section is to be delivered, the date on which such item was given to such trade or business for delivery; and
- (iii) Provides overnight or 2-day delivery service throughout the United States.

(2) FDA may periodically issue guidance regarding designated delivery services.

5. Section 314.53 is revised to read as follows:

§ 314.53 Submission of patent information.

(a) Who must submit patent information. This section applies to any applicant who submits to FDA an NDA or an amendment to it under section 505(b) of the Federal Food, Drug,

and Cosmetic Act and § 314.50 or a supplement to an approved NDA under § 314.70, except as provided in paragraph (d)(2) of this section.

(b) Patents for which information must be submitted and patents for which information must not be submitted--(1) General requirements. An applicant described in paragraph (a) of this section must submit to its NDA the required information, on the required FDA declaration form, set forth in paragraph (c) of this section for each patent that claims the drug or a method of using the drug that is the subject of the NDA or amendment or supplement to it and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. For purposes of this part, such patents consist of drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents. For patents that claim the drug substance, the applicant must submit information only on those patents that claim the drug substance that is the subject of the pending or approved NDA or that claim a drug substance that is the same as the active ingredient that is the subject of the approved or pending NDA. For patents that claim only a polymorph that is the same as the active ingredient described in the approved or pending NDA, the applicant must certify in the required FDA declaration form that the applicant has test data, as set forth in paragraph (b)(2) of this section, demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA. For patents that claim a drug product, the applicant must submit information only on those patents that claim the drug product, as is defined in § 314.3, that is described in the pending or approved NDA. For patents that claim a method of use, the applicant must submit information only on those patents that claim indications or other conditions of use for which approval is sought or has been granted in the NDA. The applicant must separately identify each



pending or approved method of use and related patent claim(s). For approved NDAs, the NDA holder's description of the patented method of use required by paragraph (c)(2)(ii)(P)(3) of this section must describe only the approved method(s) of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. If the method(s) of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, the applicant must describe only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. For approved NDAs, the NDA holder submitting information on the method-of-use patent must identify with specificity the section(s) and subsection(s) of the approved labeling that describes the method(s) of use claimed by the patent submitted. Process patents, patents claiming packaging, patents claiming metabolites, and patents claiming intermediates are not covered by this section, and information on these patents must not be submitted to FDA.

(2) Test data for submission of patent information for patents that claim only a polymorph. The test data, referenced in paragraph (b)(1) of this section, must include the following:

(i) A full description of the polymorphic form of the drug substance, including its physical and chemical characteristics and stability; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the polymorphic form of the drug substance;

(ii) The executed batch record for a drug product containing the polymorphic form of the drug substance and documentation that the batch was manufactured under current good manufacturing practice requirements;

(iii) Demonstration of bioequivalence between the executed batch of the drug product that contains the polymorphic form of the drug substance and the drug product as described in the NDA;

(iv) A list of all components used in the manufacture of the drug product containing the polymorphic form and a statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; a description of the manufacturing and packaging procedures and in-process controls for the drug product; such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity, and bioavailability of the drug product, including release and stability data complying with the approved product specifications to demonstrate pharmaceutical equivalence and comparable product stability; and

(v) Comparative in vitro dissolution testing on 12 dosage units each of the executed test batch and the NDA product.

(c) Reporting requirements--(1) General requirements. An applicant described in paragraph (a) of this section must submit the required patent information described in paragraph (c)(2) of this section for each patent that meets the requirements described in paragraph (b) of this section. We will not accept the patent information unless it is submitted on the appropriate form, Form FDA 3542 or 3542a, and contains the information required in paragraph (c)(2) of this section. These forms may be obtained on the Internet at <http://www.fda.gov> by searching for “forms”.

(2) Drug substance (active ingredient), drug product (formulation or composition), and method-of-use patents--(i) Original declaration. For each patent that claims a drug substance (active ingredient), drug product (formulation and composition), or method of use, the applicant must submit Form FDA 3542a. The following information and verification is required, subject to the exceptions listed in paragraph (c)(2)(i)(S) of this section:

(A) NDA number;

(B) The NDA applicant's name, full address, phone number and, if available, fax number and email address;

(C) Trade name (or proposed trade name) of new drug;

(D) Active ingredient(s) of new drug;

(E) Strength(s) of new drug;

(F) Dosage form(s) and route(s) of administration of new drug, and whether the applicant proposes to market the new drug for prescription use or over-the-counter use;

(G) U.S. patent number, issue date, and expiration date of patent submitted;

(H) The patent owner's name, full address, phone number and, if available, fax number and email address;

(I) The name, full address, phone number and, if available, fax number and email address of an agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and §§ 314.52 and 314.95 (if patent owner or NDA applicant or holder does not reside or have a place of business within the United States);

(J) Information on whether the patent has been submitted previously for the NDA or supplement;

(K) If the patent has been submitted previously for listing, identify all change(s) from the previously submitted patent information and specify whether the change is related to the patent or related to an FDA action or procedure;

(L) Information on whether the patent is a product-by-process patent in which the product claimed is novel;

(M) Information on the drug substance (active ingredient) patent, including the following:

(1) Whether the patent claims a drug substance that is an active ingredient in the drug product described in the NDA or supplement;

(2) Whether the patent claims only a polymorph that is the same active ingredient that is described in the pending NDA or supplement;

(3) Whether the applicant has test data, described in paragraph (b)(2) of this section, demonstrating that a drug product containing only the polymorph will perform the same as the drug product described in the NDA or supplement, and a description of the polymorphic form(s) claimed by the patent for which such test data exist;

(4) Whether the patent claims only a metabolite of the active ingredient; and

(5) Whether the patent claims only an intermediate;

(N) Information on the drug product (composition/formulation) patent, including the following:

(1) Whether the patent claims the drug product for which approval is being sought, as defined in § 314.3; and

(2) Whether the patent claims only an intermediate;

(O) Information on each method-of-use patent, including the following:

(1) Whether the patent claims one or more methods of using the drug product for which approval is being sought and a description of each pending method of use and related patent claim of the patent being submitted;

(2) Identification of the specific section(s) and subsection(s) of the proposed labeling for the drug product that describes the method of use claimed by the patent submitted; and

(3) An applicant that submits information for a patent that claims one or more methods of using the drug product must also submit information described in either paragraph (c)(2)(i)(M) or (N) of this section, regarding whether that patent also claims either the drug substance (active ingredient) or the drug product (composition/formulation).

(P) Whether there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition), or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product;

(Q) A signed verification that states:

The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

(R) Information on whether the applicant, patent owner or attorney, agent, representative, or other authorized official signed the form; the name of the person; and the full address, phone number and, if available, the fax number and email address; and

(S) Exceptions to required submission of patent information:

(1) If an applicant submits the information described in paragraph (c)(2)(i)(M) of this section for a patent that claims the drug substance (active ingredient) and meets the requirements for listing on that basis, then the applicant is not required to provide the information described in paragraph (c)(2)(i)(N) of this section on whether that patent also claims the drug product (composition/formulation);

(2) If an applicant submits the information described in paragraph (c)(2)(i)(N) of this section for a patent that claims the drug product (composition/formulation) and meets the requirements for listing on that basis, then the applicant is not required to provide the information described in paragraph (c)(2)(i)(M) of this section on whether that patent also claims the drug substance (active ingredient);

(3) If the applicant submits a supplement for a change other than one of the changes listed under paragraph (d)(2)(i) of this section, then the patent information submission requirements of paragraph (d)(2)(ii) of this section apply.

(ii) Submission of patent information upon and after approval. Within 30 days after the date of approval of its NDA or supplement, the applicant must submit Form FDA 3542 for each patent that claims the drug substance (active ingredient), drug product (formulation and composition), or approved method of use. FDA will not list or publish patent information if it is not provided on this form or if the patent declaration does not contain the required information or indicates the patent is not eligible for listing. Patent information must also be submitted for patents issued after the date of approval of the NDA as required in paragraph (c)(2)(ii) of this section. As described in paragraph (d)(3) of this section, to be timely filed, patent information for patents issued after the date of approval of the NDA must be submitted to FDA within 30 days of the date of issuance of the patent. If the applicant submits the required patent

information within the 30 days, but we notify an applicant that a declaration form is incomplete or shows that the patent is not eligible for listing, the applicant must submit an acceptable declaration form within 15 days of FDA notification to be considered timely filed. The following information and verification statement is required, subject to the exceptions listed in paragraph (c)(2)(ii)(T) of this section:

- (A) NDA number;
- (B) The NDA holder's name, full address, phone number and, if available, fax number and email address;
- (C) Trade name of new drug;
- (D) Active ingredient(s) of new drug;
- (E) Strength(s) of new drug;
- (F) Dosage form(s) and route(s) of administration of new drug, and whether the new drug is approved for prescription use or over-the-counter use;
- (G) Approval date of NDA or supplement;
- (H) U.S. patent number, issue date, and expiration date of patent submitted;
- (I) The patent owner's name, full address, phone number and, if available, fax number and email address;
- (J) The name, full address, phone number and, if available, fax number and email address of an agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and §§ 314.52 and 314.95 (if patent owner or NDA applicant or holder does not reside or have a place of business within the United States);

(K) Information on whether the patent has been submitted previously for the NDA or supplement;

(L) If the patent has been submitted previously for listing, identify all change(s) from the previously submitted patent information and specify whether the change is related to the patent or related to an FDA action or procedure;

(M) Information on whether the patent is a product-by-process patent in which the product claimed is novel;

(N) Information on the drug substance (active ingredient) patent, including the following:

(1) Whether the patent claims a drug substance that is an active ingredient in the drug product described in the approved NDA;

(2) Whether the patent claims only a polymorph that is the same as the active ingredient that is described in the approved NDA;

(3) Whether the applicant has test data, described in paragraph (b)(2) of this section, demonstrating that a drug product containing only the polymorph will perform the same as the drug product described in the approved NDA and a description of the polymorphic form(s) claimed by the patent for which such test data exist;

(4) Whether the patent claims only a metabolite of the active ingredient; and

(5) Whether the patent claims only an intermediate;

(O) Information on the drug product (composition/formulation) patent, including the following:

(1) Whether the patent claims the approved drug product as defined in § 314.3; and

(2) Whether the patent claims only an intermediate;

(P) Information on each method-of-use patent, including the following:



(1) Whether the patent claims one or more approved methods of using the approved drug product and a description of each approved method of use and related patent claim of the patent being submitted;

(2) Identification of the specific section(s) and subsection(s) of the approved labeling for the drug product that describes the method of use claimed by the patent submitted;

(3) The description of the patented method of use as required for publication, which must contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method-of-use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval (for example, if the method(s) of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, then the applicant must describe only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product); and

(4) An applicant that submits information for a patent that claims one or more methods of using the drug product must also submit information described in either paragraph (c)(2)(ii)(N) or (O) of this section, regarding whether that patent also claims either the drug substance (active ingredient) or the drug product (composition/formulation).

(Q) Whether there are no relevant patents that claim the approved drug substance (active ingredient), the approved drug product (formulation or composition), or approved method(s) of use and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product;

(R) A signed verification that states:

The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information or response to a request under 21 CFR 314.53(f)(1) is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

(S) Information on whether the applicant, patent owner or attorney, agent, representative, or other authorized official signed the form; the name of the person; and the full address, phone number and, if available, the fax number and email address; and

(T) Exceptions to required submission of patent information:

(1) If an applicant submits the information described in paragraph (c)(2)(ii)(N) of this section for a patent that claims the drug substance (active ingredient) and meets the requirements for listing on that basis, then the applicant is not required to provide the information described in paragraph (c)(2)(ii)(O) of this section on whether that patent also claims the drug product (composition/formulation).

(2) If an applicant submits the information described in paragraph (c)(2)(ii)(O) of this section for a patent that claims the drug product (composition/formulation) and meets the requirements for listing on that basis, then the applicant is not required to provide the information described in paragraph (c)(2)(ii)(N) of this section on whether that patent also claims the drug substance (active ingredient).

(3) If the applicant submits a supplement for a change other than one of the changes listed under paragraph (d)(2)(i) of this section, then the patent information submission requirements of paragraph (d)(2)(ii) of this section apply.

(3) No relevant patents. If the applicant believes that there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition), or the

method(s) of use for which the applicant has received approval, and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product, the applicant will verify this information in the appropriate form, Form FDA 3542 or 3542a.

(4) Authorized signature. The declarations required by this section must be signed by the applicant or patent owner, or the applicant's or patent owner's attorney, agent (representative), or other authorized official.

(d) When and where to submit patent information--(1) Original NDA. An applicant must submit with its original NDA submitted under this part, the information described in paragraph (c) of this section on each drug substance (active ingredient), drug product (formulation and composition), and method-of-use patent issued before the NDA is filed with FDA and for which patent information is required to be submitted under this section. If a patent is issued after the NDA is filed with FDA but before the NDA is approved, the applicant must, within 30 days of the date of issuance of the patent, submit the required patent information in an amendment to the NDA under § 314.60.

(2) Supplements. (i) An applicant must submit patent information required under paragraph (c) of this section for a patent that claims the drug substance, drug product, or method of use for which approval is sought in any of the following supplements:

- (A) To add or change the dosage form or route of administration;
- (B) To add or change the strength; or
- (C) To change the drug product from prescription use to over-the-counter use.

(ii) If the applicant submits a supplement for a change other than one of the changes listed under paragraph (d)(2)(i) of this section (for example, to change the formulation, to add a

new indication or other condition of use, or to make any other patented change regarding the drug substance, drug product, or any method of use), the following patent information submission requirements apply:

(A) If existing patents for which information required by paragraph (c) of this section has already been submitted to FDA for the product approved in the original NDA claim the changed product, the applicant is not required to resubmit this patent information pursuant to paragraph (c) of this section unless the published description of the patented method of use would change upon approval of the supplement, and FDA will continue to list this patent information for the product;

(B) If one or more existing patents for which information has already been submitted to FDA no longer claim the changed product, the applicant must submit a request under paragraph (f)(2)(iv) of this section to remove that patent information from the list at the time of approval of the supplement;

(C) If one or more existing drug substance (active ingredient), drug product (formulation and composition), or method-of-use patents claim the changed product for which approval is sought in the supplement and such patent information has not been submitted to FDA, the applicant must submit the patent information required under paragraph (c) of this section.

(3) Newly issued patents. If a patent is issued for a drug substance, drug product, or method of use after an NDA is approved, the applicant must submit to FDA, as described in paragraph (d)(4) of this section, the required patent information within 30 days of the date of issuance of the patent. If the required patent information is not submitted within 30 days of the issuance of the patent, FDA will list the patent, but patent certifications or statements will be

governed by the provisions regarding untimely filed patent information at §§ 314.50(i)(4) and (6) and 314.94(a)(12)(vi) and (viii).

(4) Submission of Forms FDA 3542a and 3542--(i) Patent information submitted with the filing of an NDA, amendment, or supplement. The applicant must submit patent information required by paragraphs (c)(1) and (c)(2)(i) of this section and § 314.50(h) or § 314.70(f) on Form FDA 3542a to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266, or to FDA in an electronic format submission that complies with § 314.50(l)(5). Form FDA 3542a should not be submitted to the Orange Book Staff in the Office of Generic Drugs.

(ii) Patent information submitted upon and after approval of an NDA or supplement. The applicant must submit patent information required by paragraphs (c)(1) and (c)(2)(ii) of this section on Form FDA 3542 to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266, or to FDA in an electronic format submission that complies with § 314.50(l)(5). Form FDA 3542 should not be submitted to the Orange Book Staff in the Office of Generic Drugs.

(5) Submission date. Patent information will be considered to be submitted to FDA for purposes of paragraph (d)(3) of this section as of the earlier of the date the information submitted on Form FDA 3542 is date-stamped by the Central Document Room, or officially received by FDA in an electronic format submission that complies with § 314.50(l)(5).

(6) Identification. Each submission of patent information, except information submitted with an original NDA, must bear prominent identification as to its contents, i.e., “Patent Information,” or, if submitted after approval of an NDA, “Time Sensitive Patent Information.”

(e) Public disclosure of patent information. FDA will publish in the list the patent number and expiration date of each patent that is required to be, and is, submitted to FDA by an applicant, and for each method-of-use patent, the description of the method of use claimed by the patent as required by § 314.53(c)(2)(ii)(P)(3). FDA will publish such patent information upon approval of the NDA, or, if the patent information is submitted by the applicant after approval of an NDA as provided under paragraph (d)(2) of this section, as soon as possible after the submission to the Agency of the patent information. A request for copies of the submitted patent information must be sent in writing to the Freedom of Information Staff at the address listed on the Agency's Web site at <http://www.fda.gov>. The submitted patent information, and requests to remove a patent or patent information from the list, may be subject to public disclosure.

(f) Correction of patent information errors--(1) Requests by persons other than the NDA holder. If any person disputes the accuracy or relevance of patent information submitted to the Agency under this section and published by FDA in the list, or believes that an NDA holder has failed to submit required patent information, that person must first notify the Agency in a written or electronic communication titled "314.53(f) Patent Listing Dispute." The patent listing dispute communication must include a statement of dispute that describes the specific grounds for disagreement regarding the accuracy or relevance of patent information for FDA to send to the applicable NDA holder. For a dispute regarding the accuracy or relevance of patent information regarding an approved method of using the drug product, this statement of dispute must be only a narrative description (no more than 250 words) of the person's interpretation of the scope of the patent. This statement of dispute must only contain information for which the person consents to disclosure because FDA will send the text of the statement to the applicable NDA holder without review or redaction. The patent listing dispute communication should be directed to the Office

of Generic Drugs, OGD Document Room, Attention: Orange Book Staff, 7620 Standish Pl., Rockville, MD 20855, or to the Orange Book Staff at the email address listed on the Agency's Web site at <http://www.fda.gov>.

(i) Communication with the NDA holder--(A) Drug substance or drug product claim. For requests submitted under this paragraph (f)(1) that are directed to the accuracy or relevance of submitted patent information regarding a drug substance or drug product claim, the Agency will send the statement of dispute to the applicable NDA holder. The NDA holder must confirm the correctness of the patent information and include the signed verification required by paragraph (c)(2)(ii)(R) of this section or withdraw or amend the patent information in accordance with paragraph (f)(2) of this section within 30 days of the date on which the Agency sends the statement of dispute. Unless the NDA holder withdraws or amends its patent information in response to the patent listing dispute, the Agency will not change the patent information in the Orange Book.

(B) Method-of-use claim. For requests submitted under this paragraph (f)(1) that are directed to the accuracy or relevance of submitted patent information regarding an approved method of using the drug product, FDA will send the statement of dispute to the NDA holder. The NDA holder must confirm the correctness of its description of the approved method of use claimed by the patent that has been included as the "Use Code" in the Orange Book, or withdraw or amend the patent information in accordance with paragraph (f)(2) of this section, provide a narrative description (no more than 250 words) of the NDA holder's interpretation of the scope of the patent that explains why the existing or amended "Use Code" describes only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the

manufacture, use, or sale of the drug product, and include the signed verification required by paragraph (c)(2)(ii)(R) of this section within 30 days of the date on which the Agency sends the statement of dispute. The narrative description must only contain information for which the NDA holder consents to disclosure because FDA will send the text of the statement to the person who submitted the patent listing dispute without review or redaction.

(1) If the NDA holder confirms the correctness of the patent information, provides the narrative description required by paragraph (f)(1)(i)(B) of this section, and includes the signed verification required by paragraph (c)(2)(ii)(R) of this section within 30 days of the date on which the Agency sends the statement of dispute, the Agency will not change the patent information in the Orange Book.

(2) If the NDA holder responds to the patent listing dispute with amended patent information in accordance with paragraph (f)(2) of this section, provides the narrative description required by paragraph (f)(1)(i)(B) of this section, and includes the signed verification required by paragraph (c)(2)(ii)(R) of this section within 30 days of the date on which the Agency sends the statement of dispute, FDA will update the Orange Book to reflect the amended patent information.

(ii) Patent certification or statement during and after patent listing dispute. A 505(b)(2) application or ANDA must contain an appropriate certification or statement for each listed patent, including the disputed patent, during and after the patent listing dispute.

(iii) Information on patent listing disputes. FDA will promptly post information on its Web site regarding whether a patent listing dispute has been submitted for a published description of a patented method of use for a drug product and whether the NDA holder has timely responded to the patent listing dispute.



(2) Requests by the NDA holder--(i) Patents or patent claims that no longer meet the statutory requirements for listing. If the NDA holder determines that a patent or patent claim no longer meets the requirements for listing in section 505(b)(1) or (c)(2) of the Federal Food, Drug, and Cosmetic Act (including if there has been a judicial finding of invalidity for a listed patent, from which no appeal has been or can be taken), the NDA holder is required to promptly notify FDA to amend the patent information or withdraw the patent or patent information and request that the patent or patent information be removed from the list. If the NDA holder is required by court order to amend patent information or withdraw a patent from the list, it must submit an amendment to its NDA that includes a copy of the order, within 14 days of the date the order was entered, to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266. The amendment to the NDA must bear the identification described in paragraph (d)(6) of this section. FDA will remove a patent or patent information from the list if there is no first applicant eligible for 180-day exclusivity based on a paragraph IV certification to that patent or after the 180-day exclusivity period of a first applicant based on that patent has expired or has been extinguished.

(ii) Patent term restoration. If the term of a listed patent is extended pursuant to 35 U.S.C. 156(e), the NDA holder must submit on Form FDA 3542 a correction to the expiration date of the patent. This correction must be submitted within 30 days of receipt of a certificate of extension as described in 35 U.S.C. 156(e)(1) or documentation of an extension of the term of the patent as described in 35 U.S.C. 156(e)(2).

(iii) Submission of corrections or changes to patent information. Corrections or changes to previously submitted patent information, other than withdrawal of a patent and requests to remove a patent from the list, must be submitted on Form FDA 3542 or 3542a, as appropriate, in

an amendment or supplement to the NDA. The amendment or supplement to the NDA must bear the identification described in paragraph (d)(6) of this section. We will not accept the corrections or changes unless they are submitted on the appropriate forms.

(iv) Submission of patent withdrawals and requests to remove a patent from the list.

Withdrawal of a patent and requests to remove a patent from the list must be submitted to the same addresses described in paragraph (d)(4)(ii) of this section, except that the withdrawal or request to remove a patent from the list is not required to be submitted on Form FDA 3542 and may be submitted by letter. Withdrawal of a patent and a request to remove a patent from the list must contain the following information:

- (A) The NDA number to which the request applies;
- (B) Each product(s) approved in the NDA to which the request applies; and
- (C) The patent number.

6. Amend § 314.54 as follows:

- a. Remove the word “shall” and add in its place the word “must” in paragraph (a)(1) introductory text and paragraphs (a)(1)(i) and (a)(3); and
- b. Revise the section heading, paragraph (a) introductory text, and paragraphs (a)(1)(iii), (v), and (vi), (a)(2) and (4), and (b).

The revisions read as follows:

§ 314.54 Procedure for submission of a 505(b)(2) application requiring investigations for approval of a new indication for, or other change from, a listed drug.

(a) The Federal Food, Drug, and Cosmetic Act does not permit approval of an ANDA for a new indication, nor does it permit approval of other changes in a listed drug if investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the change.

Any person seeking approval of a drug product that represents a modification of a listed drug (e.g., a new indication or new dosage form) and for which investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the changes may, except as provided in paragraph (b) of this section, submit a 505(b)(2) application. This 505(b)(2) application need contain only that information needed to support the modification(s) of the listed drug.

(1) \* \* \*

(iii) Identification of each listed drug for which FDA has made a finding of safety and effectiveness and on which finding the applicant relies in seeking approval of its proposed drug product by established name, if any, proprietary name, dosage form, strength, route of administration, name of listed drug's application holder, and listed drug's approved NDA number. The listed drug(s) identified as relied upon must include a drug product approved in an NDA that:

(A) Is pharmaceutically equivalent to the drug product for which the original 505(b)(2) application is submitted; and

(B) Was approved before the original 505(b)(2) application was submitted.

\* \* \* \* \*

(v) Any patent information required under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act with respect to any patent which claims the drug for which approval is sought or a method of using such drug and to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

(vi) Any patent certification or statement required under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act with respect to any relevant patents that claim the listed drug(s) on which investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed drug(s). A 505(b)(2) applicant seeking approval of a drug that is pharmaceutically equivalent to a listed drug approved in an NDA implicitly relies upon one such pharmaceutically equivalent listed drug.

\* \* \* \* \*

(2) The applicant must submit a review copy that contains the technical sections described in § 314.50(d)(1), except that the section described in § 314.50(d)(1)(ii)(c) must contain the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product, and § 314.50(d)(3), and the technical sections described in § 314.50(d)(2), (d)(4) through (6), and (f) when needed to support the modification. Each of the technical sections in the review copy is required to be separately bound with a copy of the information required under § 314.50(a), (b), and (c) and a copy of the proposed labeling.

\* \* \* \* \*

(4) The applicant must submit a field copy of the 505(b)(2) application that contains the technical section described in § 314.50(d)(1), a copy of the information required under § 314.50(a) and (c), and certification that the field copy is a true copy of the technical section described in § 314.50(d)(1) contained in the archival and review copies of the 505(b)(2) application.

(b) A 505(b)(2) application may not be submitted under this section for a drug product whose only difference from a listed drug is that:

(1) The extent to which its active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the listed drug; or

(2) The rate at which its active ingredient(s) is absorbed or otherwise made available to the site of action is unintentionally less than that of the listed drug.

7. Amend § 314.60 as follows:

a. Remove the word “application” and add in its place “NDA” wherever it appears;

b. Remove the word “act” and add in its place “Federal Food, Drug, and Cosmetic Act” wherever it appears in paragraphs (b)(1) and (4), (c)(1)(i), and (c)(2);

c. Remove “505(c)(3)(D)(ii)” and add in its place “505(c)(3)(E)(ii)” in paragraphs (c)(1)(i) and (c)(2);

d. Add paragraph headings in paragraphs (b) and (c);

e. Revise the section heading and paragraphs (a), (c)(1)(iii), and (d); and

f. Add paragraphs (e) and (f).

The revisions and additions read as follows:

§ 314.60 Amendments to an unapproved NDA, supplement, or resubmission.

(a) Submission of NDA. FDA generally assumes that when an original NDA, supplement to an approved NDA, or resubmission of an NDA or supplement is submitted to the Agency for review, the applicant believes that the Agency can approve the NDA, supplement, or resubmission as submitted. However, the applicant may submit an amendment to an NDA, supplement, or resubmission that has been filed under § 314.101 but is not yet approved.

(b) Submission of major amendment. \* \* \*

(c) Limitation on certain amendments.

(1) \* \* \*

(iii) The applicant has not obtained a right of reference or use to the investigation described in paragraph (c)(1)(ii) of this section; and

\* \* \* \* \*

(d) Field copy. The applicant must submit a field copy of each amendment to a section of the NDA described in § 314.50(d)(1). The applicant must include in its submission of each such amendment to FDA a statement certifying that a field copy of the amendment has been sent to the applicant's home FDA district office.

(e) Different drug. An applicant may not amend a 505(b)(2) application to seek approval of a drug that is a different drug from the drug in the original submission of the 505(b)(2) application. For purposes of this paragraph (e), a drug is a different drug if it has been modified to have a different active ingredient, different route of administration, different dosage form, or difference in excipients that requires either a separate clinical study to establish safety or effectiveness or, for topical products, that requires a separate in vivo demonstration of bioequivalence. However, notwithstanding the limitation described in this paragraph (e), an applicant may amend the 505(b)(2) application to seek approval of a different strength.

(f) Patent certification requirements. (1) An amendment to a 505(b)(2) application is required to contain an appropriate patent certification or statement described in § 314.50(i) or a recertification for a previously submitted paragraph IV certification if approval is sought for any of the following types of amendments:

- (i) To add a new indication or other condition of use;
- (ii) To add a new strength;
- (iii) To make other than minor changes in product formulation; or
- (iv) To change the physical form or crystalline structure of the active ingredient.

(2) If the amendment to the 505(b)(2) application does not contain a patent certification or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described in paragraph (f)(1) of this section.

8. Amend § 314.70 as follows:

a. Remove the word “application” and add in its place “NDA” wherever it appears in the paragraph (a) heading and paragraphs (a)(1)(i) and (ii), (b)(2)(i) and (viii), (c)(6) introductory text, (c)(7), (d)(2)(v) through (vii), (d)(3)(i), and (e);

b. Remove the words “cover letter” and add in their place the word “submission” in paragraph (a)(6);

c. Remove the words “and its mailing cover” in paragraph (b)(4);

d. Revise the section heading and paragraphs (a)(2) and (f); and

e. Add paragraph (h).

The revisions and addition read as follows:

§ 314.70 Supplements and other changes to an approved NDA.

(a) \* \* \*

(2) The NDA holder must assess the effects of the change before distributing a drug product made with a manufacturing change.

\* \* \* \* \*

(f) Patent information. The applicant must comply with the patent information requirements under section 505(c)(2) of the Federal Food, Drug, and Cosmetic Act and § 314.53.

\* \* \* \* \*

(h) Different drug. An applicant may not supplement a 505(b)(2) application to seek approval of a drug that is a different drug from the drug in the approved 505(b)(2) application.

For purposes of this paragraph (h), a drug is a different drug if it has been modified to have a different active ingredient, different route of administration, different dosage form, or difference in excipients that requires either a separate clinical study to establish safety or effectiveness or, for topical products, that requires a separate in vivo demonstration of bioequivalence. However, notwithstanding the limitation described in this paragraph (h), an applicant may supplement the 505(b)(2) application to seek approval of a different strength.

9. Amend § 314.90 by removing the word “application” and adding in its place “NDA” wherever it appears and adding paragraph (c) to read as follows:

§ 314.90 Waivers.

\* \* \* \* \*

(c) If FDA grants the applicant’s waiver request with respect to a requirement under §§ 314.50 through 314.81, the waived requirement will not constitute a basis for refusal to approve an NDA under § 314.125.

10. Amend § 314.93 as follows:

- a. Remove the words “abbreviated new drug applications” and add in their place “ANDAs” in paragraph (a);
- b. Remove the words “abbreviated new drug application” and add in their place “ANDA” wherever they appear in paragraphs (b), (c), and (e)(3);
- c. Remove the words “abbreviated application” and add in their place “ANDA” in paragraph (b);
- d. Remove “201(b)” and add in its place “201(p)” in paragraph (d)(3);
- e. Remove the word “act” and add in its place “Federal Food, Drug, and Cosmetic Act” in paragraphs (d)(3) and (e)(1)(iii)(C);



- f. Remove the period at the end of paragraph (e)(1)(v) and add in its place “; or”;
- g. Add paragraph (e)(1)(vi);
- h. Redesignate paragraph (f) as paragraph (f)(1); and
- i. Add paragraph (f)(2).

The revisions and additions read as follows:

§ 314.93 Petition to request a change from a listed drug.

\* \* \* \* \*

(e) \* \* \*

(1) \* \* \*

(vi) A drug product is approved in an NDA for the change described in the petition.

\* \* \* \* \*

(f) \* \* \*

(2) If, after approval of a petition and before approval of an ANDA submitted pursuant to the approved petition, a drug product is approved in an NDA for the change described in the petition, the petition and the listed drug identified in the petition can no longer be the basis for ANDA submission, irrespective of whether FDA has withdrawn approval of the petition. A person seeking approval for such drug product must submit a new ANDA that identifies the pharmaceutically equivalent reference listed drug as the basis for ANDA submission and comply with applicable regulatory requirements.

11. Amend § 314.94 as follows:

a. Remove the words “abbreviated application” and add in their place “ANDA” wherever they appear in paragraphs (a)(1), (a)(5)(ii)(A), (a)(6)(ii), (a)(9)(v), (a)(12)(i)(A)(4), (a)(13), (d)(1)(i), (d)(4), and (d)(5);

b. Remove the words “abbreviated new drug application” and add in their place “ANDA” wherever they appear in paragraph (a) introductory text and paragraphs (a)(8)(i) and (b);

c. Remove the word “shall” and add in its place the word “must” wherever it appears in paragraph (a) introductory text and paragraphs (a)(1), (a)(9)(ii) through (iv), (a)(12)(i)(A)(1) through (3), (a)(13), (b), and (d)(5);

d. Remove the word “act” and add in its place “Federal Food, Drug, and Cosmetic Act” wherever it appears in paragraphs (a)(5)(ii)(A), (a)(7)(ii)(C), and (a)(8)(iv);

e. Remove “§ 320.1(g) of this chapter” and add in its place “§ 314.3(b)” in paragraph (a)(7)(i);

f. Remove and reserve paragraph (a)(12)(iv); and

g. Revise the section heading and the introductory text, paragraph (a) heading, paragraph (a)(2), paragraph (a)(3), the first sentence of paragraph (a)(7)(ii) introductory text, paragraphs (a)(7)(iii) and (a)(9)(i), paragraph (a)(12)(i) heading, paragraph (a)(12)(i)(A) introductory text, paragraphs (a)(12)(i)(A)(4), (a)(12)(i)(B), (a)(12)(ii) and (iii), (a)(12)(iv) through (viii), paragraph (d) heading, paragraph (d)(1) introductory text, and paragraph (d)(2).

The revisions read as follows:

§ 314.94 Content and format of an ANDA.

ANDAs are required to be submitted in the form and contain the information required under this section. Three copies of the ANDA are required, an archival copy, a review copy, and a field copy. FDA will maintain guidance documents on the format and content of ANDAs to assist applicants in their preparation.

(a) ANDAs. \* \* \*

\* \* \* \* \*

(2) Table of contents. The archival copy of the ANDA is required to contain a table of contents that shows the volume number and page number of the contents of the submission.

(3) Basis for ANDA submission. An ANDA must refer to a listed drug. Ordinarily, that listed drug will be the drug product selected by the Agency as the reference standard for conducting bioequivalence testing. The ANDA must contain:

(i) The name of the reference listed drug, including its dosage form and strength. For an ANDA based on an approved petition under § 10.30 of this chapter and § 314.93, the reference listed drug must be the same as the listed drug referenced in the approved petition.

(ii) A statement as to whether, according to the information published in the list, the reference listed drug is entitled to a period of marketing exclusivity under section 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act.

(iii) For an ANDA based on an approved petition under § 10.30 of this chapter and § 314.93, a reference to the FDA-assigned docket number for the petition and a copy of FDA's correspondence approving the petition.

\* \* \* \*

(7) \* \* \*

(ii) If the ANDA is submitted pursuant to a petition approved under § 314.93, the results of any bioavailability or bioequivalence testing required by the Agency, or any other information required by the Agency to show that the active ingredients of the proposed drug product are of the same pharmacological or therapeutic class as those in the reference listed drug and that the proposed drug product can be expected to have the same therapeutic effect as the reference listed drug. \* \* \*

\* \* \* \*

(iii) For each in vivo or in vitro bioequivalence study contained in the ANDA:

(A) A description of the analytical and statistical methods used in each study; and

(B) With respect to each study involving human subjects, a statement that the study either was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to the regulations under § 56.104 or § 56.105 of this chapter, and that it was conducted in compliance with the informed consent regulations in part 50 of this chapter.

\* \* \* \*

(9) \* \* \*

(i) The information required under § 314.50(d)(1), except that the information required under § 314.50(d)(1)(ii)(c) must contain the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product.

\* \* \* \*

(12) Patent certification--(i) Patents claiming drug substance, drug product, or method of use. (A) An appropriate patent certification or statement with respect to each patent issued by the U. S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the reference listed drug or that claims a use of such listed drug for which the applicant is seeking approval under section 505(j) of the Federal Food, Drug, and Cosmetic Act and for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53. For each such patent, the applicant must provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

\* \* \* \*

(4)(i) That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted. The applicant must entitle such a certification “Paragraph IV Certification”. This certification must be submitted in the following form:

I, (name of applicant), certify that Patent No. \_\_\_\_\_ (is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of) (name of proposed drug product) for which this ANDA is submitted.

(ii) The certification must be accompanied by a statement that the applicant will comply with the requirements under § 314.95(a) with respect to providing a notice to each owner of the patent or its representative and to the NDA holder (or, if the NDA holder does not reside or maintain a place of business within the United States, its attorney, agent, or other authorized official) for the listed drug, with the requirements under § 314.95(b) with respect to sending the notice, and with the requirements under § 314.95(c) with respect to the content of the notice.

(B) If the ANDA refers to a listed drug that is itself a licensed generic product of a patented drug first approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act, an appropriate patent certification or statement under paragraph (a)(12)(i) and/or (iii) of this section with respect to each patent that claims the first-approved patented drug or that claims a use for such drug.

(ii) No relevant patents. If, in the opinion of the applicant and to the best of its knowledge, there are no patents described in paragraph (a)(12)(i) of this section, a certification in the following form:

In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the listed drug referred to in this ANDA or that claim a use of the listed drug.

(iii) Method-of-use patent. (A) If patent information is submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include an indication or other condition of use that is covered by the method-of-use patent, a statement explaining that the method-of-use patent does not claim a proposed indication or other condition of use.

(B) If the labeling of the drug product for which the applicant is seeking approval includes an indication or other condition of use that, according to the patent information submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53 or in the opinion of the applicant, is claimed by a method-of-use patent, an applicable certification under paragraph (a)(12)(i) of this section.

(iv) [Reserved]

(v) Licensing agreements. If the ANDA is for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, the applicant must submit a paragraph IV certification as to that patent and a statement that the applicant has been granted a patent license. If the patent owner consents to approval of the ANDA (if otherwise eligible for approval) as of a specific date, the ANDA must contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to approval of the ANDA as of a specific date.

(vi) Untimely filing of patent information. (A) If a patent on the listed drug is issued and the holder of the approved NDA for the listed drug does not file with FDA the required information on the patent within 30 days of issuance of the patent, an applicant who submitted an ANDA for that drug that contained an appropriate patent certification or statement before the

submission of the patent information is not required to submit a patent certification or statement to address the patent or patent information that is late-listed with respect to the pending ANDA. Except as provided in § 314.53(f)(1), an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will be considered untimely filing of patent information unless:

(1) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of patent issuance;

(2) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of approval of a corresponding change to product labeling; or

(3) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of a decision by the U.S. Patent and Trademark Office or by a Federal district court, the Court of Appeals for the Federal Circuit, or the U.S. Supreme Court that is specific to the patent and alters the construction of a method-of-use claim(s) of the patent, and the amendment contains a copy of the decision.

(B) An applicant whose ANDA is submitted after the NDA holder's untimely filing of patent information, or whose pending ANDA was previously submitted but did not contain an appropriate patent certification or statement at the time of the patent submission, must submit a certification under paragraph (a)(12)(i) of this section and/or a statement under paragraph (a)(12)(iii) of this section as to that patent.

(vii) Disputed patent information. If an applicant disputes the accuracy or relevance of patent information submitted to FDA, the applicant may seek a confirmation of the correctness of the patent information in accordance with the procedures under § 314.53(f). Unless the patent

information is withdrawn, the applicant must submit an appropriate certification or statement for each listed patent.

(viii) Amended certifications. A patent certification or statement submitted under paragraphs (a)(12)(i) through (iii) of this section may be amended at any time before the approval of the ANDA. If an applicant with a pending ANDA voluntarily makes a patent certification for an untimely filed patent, the applicant may withdraw the patent certification for the untimely filed patent. An applicant must submit an amended certification as an amendment to a pending ANDA. Once an amendment is submitted to change a certification, the ANDA will no longer be considered to contain the prior certification.

(A) After finding of infringement. An applicant who has submitted a paragraph IV certification and is sued for patent infringement must submit an amendment to change its certification if a court enters a final decision from which no appeal has been or can be taken, or signs and enters a settlement order or consent decree in the action that includes a finding that the patent is infringed, unless the final decision, settlement order, or consent decree also finds the patent to be invalid. In its amendment, the applicant must certify under paragraph (a)(12)(i)(A)(3) of this section that the patent will expire on a specific date or, with respect to a patent claiming a method of use, the applicant may instead provide a statement under paragraph (a)(12)(iii) of this section if the applicant amends its ANDA such that the applicant is no longer seeking approval for a method of use claimed by the patent. Once an amendment for the change has been submitted, the ANDA will no longer be considered to contain a paragraph IV certification to the patent. If a final judgment finds the patent to be invalid and infringed, an amended certification is not required.



(B) After request to remove a patent or patent information from the list. If the list reflects that an NDA holder has requested that a patent or patent information be removed from the list and no ANDA applicant is eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent or patent information will be removed and any applicant with a pending ANDA (including a tentatively approved ANDA) who has made a certification with respect to such patent must submit an amendment to withdraw its certification. In the amendment, the applicant must state the reason for withdrawing the certification or statement (that the patent has been removed from the list). If the list reflects that an NDA holder has requested that a patent or patent information be removed from the list and one or more first applicants are eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent will remain listed until any 180-day exclusivity based on that patent has expired or has been extinguished. After any applicable 180-day exclusivity has expired or has been extinguished, the patent or patent information will be removed and any applicant with a pending ANDA (including a tentatively approved ANDA) who has made a certification with respect to such patent must submit an amendment to withdraw its certification. Once an amendment to withdraw the certification has been submitted, the ANDA will no longer be considered to contain a paragraph IV certification to the patent. If removal of a patent from the list results in there being no patents listed for the listed drug identified in the ANDA, the applicant must submit an amended certification reflecting that there are no relevant patents.

(C) Other amendments. (1) Except as provided in paragraphs (a)(12)(vi) and (a)(12)(viii)(C)(2) of this section:

(i) An applicant must amend a submitted certification or statement if, at any time before the date of approval of the ANDA, the applicant learns that the submitted certification or statement is no longer accurate; and

(ii) An applicant must submit an appropriate patent certification or statement under paragraph (a)(12)(i) and/or (iii) of this section if, after submission of the ANDA, a new patent is issued by the U.S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the reference listed drug or that claims an approved use for such reference listed drug and for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53. For a paragraph IV certification, the certification must not be submitted earlier than the first working day after the day the patent is published in the list.

(2) An applicant is not required to submit a supplement to change a submitted certification when information on a patent on the listed drug is submitted after the approval of the ANDA.

\* \* \* \* \*

(d) Format of an ANDA. (1) The applicant must submit a complete archival copy of the ANDA as required under paragraphs (a) and (c) of this section. FDA will maintain the archival copy during the review of the ANDA to permit individual reviewers to refer to information that is not contained in their particular technical sections of the ANDA, to give other Agency personnel access to the ANDA for official business, and to maintain in one place a complete copy of the ANDA.

\* \* \* \* \*

(2) For ANDAs, the applicant must submit a review copy of the ANDA that contains two separate sections. One section must contain the information described under paragraphs (a)(2) through (6) and (8) and (9) of this section and section 505(j)(2)(A)(vii) of the Federal Food, Drug, and Cosmetic Act and a copy of the analytical procedures and descriptive information needed by FDA's laboratories to perform tests on samples of the proposed drug product and to validate the applicant's analytical procedures. The other section must contain the information described under paragraphs (a)(3), (7), and (8) of this section. Each of the sections in the review copy is required to contain a copy of the application form described under paragraph (a) of this section.

\* \* \* \* \*

12. Section 314.95 is revised to read as follows:

§ 314.95 Notice of certification of invalidity, unenforceability, or noninfringement of a patent.

(a) Notice of certification. For each patent that claims the listed drug or that claims a use for such listed drug for which the applicant is seeking approval and for which the applicant submits a paragraph IV certification, the applicant must send notice of such certification by registered or certified mail, return receipt requested, or by a designated delivery service, as defined in paragraph (g) of this section to each of the following persons:

(1) Each owner of the patent that is the subject of the certification or the representative designated by the owner to receive the notice. The name and address of the patent owner or its representative may be obtained from the U.S. Patent and Trademark Office; and

(2) The holder of the approved NDA under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the listed drug that is claimed by the patent and for which the applicant is seeking approval, or, if the NDA holder does not reside or maintain a place of business within

the United States, the NDA holder's attorney, agent, or other authorized official. The name and address of the NDA holder or its attorney, agent, or authorized official may be obtained by sending a written or electronic communication to the Orange Book Staff, Office of Generic Drugs, 7620 Standish Pl., Rockville, MD 20855 or to the Orange Book Staff at the email address listed on the Agency's Web site at <http://www.fda.gov>.

(3) This paragraph (a) does not apply to a method-of-use patent that does not claim a use for which the applicant is seeking approval.

(4) An applicant may send notice by an alternative method only if FDA has agreed in advance that the method will produce an acceptable form of documentation.

(b) Sending the notice. (1) Except as provided under paragraph (d) of this section, the applicant must send the notice required by paragraph (a) of this section on or after the date it receives a paragraph IV acknowledgment letter from FDA, but not later than 20 days after the date of the postmark on the paragraph IV acknowledgment letter. The 20-day clock described in this paragraph (b) begins on the day after the date of the postmark on the paragraph IV acknowledgment letter. When the 20th day falls on Saturday, Sunday, or a Federal holiday, the 20th day will be the next day that is not a Saturday, Sunday, or Federal holiday.

(2) Any notice required by paragraph (a) of this section is invalid if it is sent before the applicant's receipt of a paragraph IV acknowledgment letter, or before the first working day after the day the patent is published in the list. The applicant will not have complied with this paragraph (b) until it sends valid notice.

(3) The applicant must submit to FDA an amendment to its ANDA that includes a statement certifying that the notice has been provided to each person identified under paragraph

(a) of this section and that the notice met the content requirements under paragraph (c) of this section. A copy of the notice itself need not be submitted to the Agency.

(c) Contents of a notice. In the notice, the applicant must cite section 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act and the notice must include, but is not limited to, the following information:

(1) A statement that FDA has received an ANDA submitted by the applicant containing any required bioavailability or bioequivalence data or information.

(2) The ANDA number.

(3) A statement that the applicant has received the paragraph IV acknowledgment letter for the ANDA.

(4) The established name, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act, of the proposed drug product.

(5) The active ingredient, strength, and dosage form of the proposed drug product.

(6) The patent number and expiration date of each listed patent for the reference listed drug alleged to be invalid, unenforceable, or not infringed.

(7) A detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed. The applicant must include in the detailed statement:

(i) For each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed.

(ii) For each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation.

(8) If the applicant alleges that the patent will not be infringed and the applicant seeks to preserve the option to later file a civil action for declaratory judgment in accordance with section 505(j)(5)(C) of the Federal Food, Drug, and Cosmetic Act, then the notice must be accompanied by an offer of confidential access to the ANDA for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the paragraph IV certification.

(9) If the applicant does not reside or have a place of business in the United States, the name and address of an agent in the United States authorized to accept service of process for the applicant.

(d) Amendment or supplement to an ANDA. (1) If, after receipt of a paragraph IV acknowledgment letter or acknowledgment letter, an applicant submits an amendment or supplement to its ANDA that includes a paragraph IV certification, the applicant must send the notice required by paragraph (a) of this section at the same time that the amendment or supplement to the ANDA is submitted to FDA, regardless of whether the applicant has already given notice with respect to another such certification contained in the ANDA or in an amendment or supplement to the ANDA.

(2) If, before receipt of a paragraph IV acknowledgment letter, an applicant submits an amendment to its ANDA that includes a paragraph IV certification, the applicant must send the notice required by paragraph (a) of this section in accordance with the procedures in paragraph (b) of this section. If an ANDA applicant's notice of its paragraph IV certification is timely provided in accordance with paragraph (b) of this section and the applicant has not submitted a previous paragraph IV certification, FDA will base its determination of whether the applicant is a first applicant on the date of submission of the amendment containing the paragraph IV certification.

(3) An applicant that submits an amendment or supplement to seek approval of a different strength must provide notice of any paragraph IV certification in accordance with paragraph (d)(1) or (2) of this section, as applicable.

(e) Documentation of timely sending and receipt of notice. The applicant must amend its ANDA to provide documentation of the date of receipt of the notice required under paragraph (a) of this section by each person provided the notice. The amendment must be submitted to FDA within 30 days after the last date on which notice was received by a person described in paragraph (a) of this section. The applicant's amendment also must include documentation that its notice was sent on a date that complies with the timeframe required by paragraph (b) or (d) of this section, as applicable, and a dated printout of the entry for the reference listed drug in FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (the list) that includes the patent that is the subject of the paragraph IV certification. FDA will accept, as adequate documentation of the date the notice was sent, a copy of the registered mail receipt, certified mail receipt, or receipt from a designated delivery service as defined in paragraph (g) of this section. FDA will accept as adequate documentation of the date of receipt a return receipt, signature proof of delivery by a designated delivery service, or a letter acknowledging receipt by the person provided the notice. An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance. A copy of the notice itself need not be submitted to the Agency.

(f) Forty-five day period after receipt of notice. If the requirements of this section are met, FDA will presume the notice to be complete and sufficient, and it will count the day following the date of receipt of the notice by the patent owner or its representative and by the approved NDA holder or its attorney, agent, or other authorized official as the first day of the 45-

day period provided for in section 505(j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act. FDA may, if the applicant provides a written statement to FDA that a later date should be used, count from such later date.

(g) Designated delivery services. (1) For purposes of this section, the term “designated delivery service” means any delivery service provided by a trade or business that the Agency determines:

- (i) Is available to the general public throughout the United States;
- (ii) Records electronically to its database, kept in the regular course of its business, or marks on the cover in which any item referred to in this section is to be delivered, the date on which such item was given to such trade or business for delivery; and
- (iii) Provides overnight or 2-day delivery service throughout the United States.

(2) FDA may periodically issue guidance regarding designated delivery services.

13. Amend § 314.96 as follows:

- a. Revise the section heading;
- b. Remove the words “abbreviated new drug application” and add in their place “ANDA” in the paragraph (a) heading and the first two sentences of paragraph (a)(1);
- c. Remove “320.1(g) of this chapter” and add in its place “314.3” in paragraph (a)(1);
- d. Remove the word “shall” and add in its place the word “must” wherever it appears and remove “to § 314.94(a)(9)” and add in its place “under § 314.94(a)(9)” in paragraph (b);
- e. Add a heading to paragraph (b); and
- f. Add paragraphs (c) and (d).

The revisions and additions read as follows:

§ 314.96 Amendments to an unapproved ANDA.



\* \* \* \* \*

(b) Field copy. \* \* \*

(c) Different listed drug. An applicant may not amend an ANDA to seek approval of a drug referring to a listed drug that is different from the reference listed drug identified in the ANDA. This paragraph (c) applies if, at any time before the approval of the ANDA, a different listed drug is approved that is the pharmaceutical equivalent to the product in the ANDA and is designated as a reference listed drug. This paragraph (c) also applies if changes are proposed in an amendment to the ANDA such that the proposed product is a pharmaceutical equivalent to a different listed drug than the reference listed drug identified in the ANDA. A change of the reference listed drug must be submitted in a new ANDA. However, notwithstanding the limitation described in this paragraph (c), an applicant may amend the ANDA to seek approval of a different strength.

(d)(1) Patent certification requirements. An amendment to an ANDA is required to contain an appropriate patent certification or statement described in § 314.94(a)(12) or a recertification for a previously submitted paragraph IV certification if approval is sought for any of the following types of amendments:

- (i) To add a new indication or other condition of use;
- (ii) To add a new strength;
- (iii) To make other than minor changes in product formulation; or
- (iv) To change the physical form or crystalline structure of the active ingredient.

(2) If the amendment to the ANDA does not contain a patent certification or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described in paragraph (d)(1) of this section.

14. Section 314.97 is revised to read as follows:

§ 314.97 Supplements and other changes to an approved ANDA.

(a) General requirements. The applicant must comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental ANDAs and other changes to an approved ANDA.

(b) Different listed drug. An applicant may not supplement an ANDA to seek approval of a drug referring to a listed drug that is different from the current reference listed drug identified in the ANDA. This paragraph (b) applies if changes are proposed in a supplement to the ANDA such that the proposed product is a pharmaceutical equivalent to a different listed drug than the reference listed drug identified in the ANDA. A change of reference listed drug must be submitted in a new ANDA. However, notwithstanding the limitation described in this paragraph (b), an applicant may supplement the ANDA to seek approval of a different strength.

15. Section 314.99 is revised to read as follows:

§ 314.99 Other responsibilities of an applicant of an ANDA.

(a) An applicant must comply with the requirements of § 314.65 regarding withdrawal by the applicant of an unapproved ANDA and § 314.72 regarding a change in ownership of an ANDA.

(b) An applicant may ask FDA to waive under this section any requirement that applies to the applicant under §§ 314.92 through 314.99. The applicant must comply with the requirements for a waiver under § 314.90. If FDA grants the applicant's waiver request with respect to a requirement under §§ 314.92 through 314.99, the waived requirement will not constitute a basis for refusal to approve an ANDA under § 314.127.

16. Section 314.101 is revised to read as follows:

§ 314.101 Filing an NDA and receiving an ANDA.

(a) Filing an NDA. (1) Within 60 days after FDA receives an NDA, the Agency will determine whether the NDA may be filed. The filing of an NDA means that FDA has made a threshold determination that the NDA is sufficiently complete to permit a substantive review.

(2) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for refusing to file the NDA apply, the Agency will file the NDA and notify the applicant in writing. In the case of a 505(b)(2) application that contains a paragraph IV certification, the applicant will be notified via a paragraph IV acknowledgment letter. The date of filing will be the date 60 days after the date FDA received the NDA. The date of filing begins the 180-day period described in section 505(c) of the Federal Food, Drug, and Cosmetic Act. This 180-day period is called the “filing clock.”

(3) If FDA refuses to file the NDA, the Agency will notify the applicant in writing and state the reason under paragraph (d) or (e) of this section for the refusal. If FDA refuses to file the NDA under paragraph (d) of this section, the applicant may request in writing within 30 days of the date of the Agency’s notification an informal conference with the Agency about whether the Agency should file the NDA. If, following the informal conference, the applicant requests that FDA file the NDA (with or without amendments to correct the deficiencies), the Agency will file the NDA over protest under paragraph (a)(2) of this section, notify the applicant in writing, and review it as filed. If the NDA is filed over protest, the date of filing will be the date 60 days after the date the applicant requested the informal conference. The applicant need not resubmit a copy of an NDA that is filed over protest. If FDA refuses to file the NDA under paragraph (e) of this section, the applicant may amend the NDA and resubmit it, and the Agency will make a determination under this section whether it may be filed.

(b)(1) Receiving an ANDA. An ANDA will be evaluated after it is submitted to determine whether the ANDA may be received. Receipt of an ANDA means that FDA has made a threshold determination that the abbreviated application is substantially complete.

(2) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for considering the ANDA not to have been received applies, the ANDA is substantially complete and the Agency will receive the ANDA and notify the applicant in writing. If FDA determines, upon evaluation, that an ANDA was substantially complete as of the date it was submitted to FDA, FDA will consider the ANDA to have been received as of the date of submission. In the case of an ANDA that contains a paragraph IV certification, the applicant will be notified via a paragraph IV acknowledgment letter.

(3) If FDA considers the ANDA not to have been received under paragraph (d) or (e) of this section, FDA will notify the applicant of the refuse-to-accept decision. The applicant may then:

- (i) Withdraw the ANDA under § 314.99; or
- (ii) Correct the deficiencies and resubmit the ANDA; or
- (iii) Take no action, in which case FDA may consider the ANDA withdrawn after 1 year.
- (c) [Reserved]

(d) NDA or ANDA deficiencies. FDA may refuse to file an NDA or may not consider an ANDA to be received if any of the following applies:

- (1) The NDA or ANDA does not contain a completed application form.
- (2) The NDA or ANDA is not submitted in the form required under § 314.50 or § 314.94.
- (3) The NDA or ANDA is incomplete because it does not on its face contain information required under section 505(b) or section 505(j) of the Federal Food, Drug, and Cosmetic Act and

§ 314.50 or § 314.94. In determining whether an ANDA is incomplete on its face, FDA will consider the nature (e.g., major or minor) of the deficiencies, including the number of deficiencies in the ANDA.

(4) The applicant fails to submit a complete environmental assessment, which addresses each of the items specified in the applicable format under § 25.40 of this chapter or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion under § 25.30 or § 25.31 of this chapter.

(5) The NDA or ANDA does not contain an accurate and complete English translation of each part of the NDA or ANDA that is not in English.

(6) The NDA or ANDA does not contain a statement for each nonclinical laboratory study that the study was conducted in compliance with the requirements set forth in part 58 of this chapter, or, for each study not conducted in compliance with part 58 of this chapter, a brief statement of the reason for the noncompliance.

(7) The NDA or ANDA does not contain a statement for each clinical study that the study was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to those regulations, and that it was conducted in compliance with the informed consent regulations in part 50 of this chapter, or, if the study was subject to but was not conducted in compliance with those regulations, the NDA or ANDA does not contain a brief statement of the reason for the noncompliance.

(8) The drug product that is the subject of the submission is already covered by an approved NDA or ANDA and the applicant of the submission:

- (i) Has an approved NDA or ANDA for the same drug product; or
- (ii) Is merely a distributor and/or repackager of the already approved drug product.

(9) The NDA is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the Federal Food, Drug, and Cosmetic Act.

(e) Regulatory deficiencies. The Agency will refuse to file an NDA or will consider an ANDA not to have been received if any of the following applies:

(1) The drug product is subject to licensing by FDA under the Public Health Service Act (42 U.S.C. 201 et seq.) and subchapter F of this chapter.

(2) Submission of a 505(b)(2) application or an ANDA is not permitted under section 505(c)(3)(E)(ii), 505(j)(5)(F)(ii), 505A(b)(1)(A)(i)(I), 505A(c)(1)(A)(i)(I), or 505E(a) of the Federal Food, Drug, and Cosmetic Act.

(f) Outcome of FDA review. (1) Within 180 days after the date of filing, plus the period of time the review period was extended (if any), FDA will either:

(i) Approve the NDA; or

(ii) Issue a notice of opportunity for a hearing if the applicant asked FDA to provide it an opportunity for a hearing on an NDA in response to a complete response letter.

(2) Within 180 days after the date of receipt, plus the period of time the review clock was extended (if any), FDA will either approve or disapprove the ANDA. If FDA disapproves the ANDA, FDA will issue a notice of opportunity for hearing if the applicant asked FDA to provide it an opportunity for a hearing on an ANDA in response to a complete response letter.

(3) This paragraph (f) does not apply to NDAs or ANDAs that have been withdrawn from FDA review by the applicant.

17. Section 314.105 is revised to read as follows:

§ 314.105 Approval of an NDA and an ANDA.

(a) FDA will approve an NDA and send the applicant an approval letter if none of the reasons in § 314.125 for refusing to approve the NDA applies. FDA will issue a tentative approval letter if an NDA otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act, but cannot be approved because there is a 7-year period of orphan exclusivity for the listed drug under section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter, or if a 505(b)(2) application otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act, but cannot be approved until the conditions in § 314.107(b)(3) are met; because there is a period of exclusivity for the listed drug under § 314.108; because there is a period of pediatric exclusivity for the listed drug under section 505A of the Federal Food, Drug, and Cosmetic Act; or because there is a period of exclusivity for the listed drug under section 505E of the Federal Food, Drug, and Cosmetic Act. A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval after any necessary additional review of the NDA. FDA's tentative approval of a drug product is based on information available to FDA at the time of the tentative approval letter (i.e., information in the 505(b)(2) application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to FDA's attention. A new drug product may not be marketed until the date of approval.

(b) FDA will approve an NDA and issue the applicant an approval letter on the basis of draft labeling if the only deficiencies in the NDA concern editorial or similar minor deficiencies in the draft labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.

(c) FDA will approve an NDA after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling, and an ANDA after it determines that the drug meets the statutory standards for manufacturing and controls, labeling, and, where applicable, bioequivalence. While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards. FDA makes its views on drug products and classes of drugs available through guidance documents, recommendations, and other statements of policy.

(d) FDA will approve an ANDA and send the applicant an approval letter if none of the reasons in § 314.127 for refusing to approve the ANDA applies. FDA will issue a tentative approval letter if an ANDA otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act, but cannot be approved because there is a 7-year period of orphan exclusivity for the listed drug under section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter, or cannot be approved until the conditions in § 314.107(b)(3) or (c) are met; because there is a period of exclusivity for the listed drug under § 314.108; because there is a period of pediatric exclusivity for the listed drug under section 505A of the Federal Food, Drug, and Cosmetic Act; or because there is a period of exclusivity for the listed drug under section 505E of the Federal Food, Drug, and Cosmetic Act. A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval after any necessary additional review of the ANDA. FDA's tentative approval of a drug product is based on information available to FDA at the time of the tentative approval letter (i.e.,



information in the ANDA and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to FDA's attention. A new drug product may not be marketed until the date of approval.

18. Section 314.107 is revised to read as follows:

§ 314.107 Date of approval of a 505(b)(2) application or ANDA.

(a) General. A drug product may be introduced or delivered for introduction into interstate commerce when the 505(b)(2) application or ANDA for the drug product is approved. A 505(b)(2) application or ANDA for a drug product is approved on the date FDA issues an approval letter under § 314.105 for the 505(b)(2) application or ANDA.

(b) Effect of patent(s) on the listed drug. As described in paragraphs (b)(1) and (2) of this section, the status of patents listed for the listed drug(s) relied upon or reference listed drug, as applicable, must be considered in determining the first possible date on which a 505(b)(2) application or ANDA can be approved. The criteria in paragraphs (b)(1) and (2) of this section will be used to determine, for each relevant patent, the date that patent will no longer prevent approval. The first possible date on which the 505(b)(2) application or ANDA can be approved will be calculated for each patent, and the 505(b)(2) application or ANDA may be approved on the last applicable date.

(1) Timing of approval based on patent certification or statement. If none of the reasons in § 314.125 or § 314.127, as applicable, for refusing to approve the 505(b)(2) application or ANDA applies, and none of the reasons in paragraph (d) of this section for delaying approval applies, the 505(b)(2) application or ANDA may be approved as follows:

(i) Immediately, if the applicant certifies under § 314.50(i) or § 314.94(a)(12) that:

(A) The applicant is aware of a relevant patent but the patent information required under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act has not been submitted to FDA; or

(B) The relevant patent has expired; or

(C) The relevant patent is invalid, unenforceable, or will not be infringed, except as provided in paragraphs (b)(3) and (c) of this section, and the 45-day period provided for in section 505(c)(3)(C) and (j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act has expired; or

(D) There are no relevant patents.

(ii) Immediately, if the applicant submits an appropriate statement under § 314.50(i) or § 314.94(a)(12) explaining that a method-of-use patent does not claim an indication or other condition of use for which the applicant is seeking approval, except that if the applicant also submits a paragraph IV certification to the patent, then the 505(b)(2) application or ANDA may be approved as provided in paragraph (b)(1)(i)(C) of this section.

(iii) On the date specified, if the applicant certifies under § 314.50(i) or § 314.94(a)(12) that the relevant patent will expire on a specified date.

(2) Patent information filed after submission of 505(b)(2) application or ANDA. If the holder of the approved NDA for the listed drug submits patent information required under § 314.53 after the date on which the 505(b)(2) application or ANDA was submitted to FDA, the 505(b)(2) applicant or ANDA applicant must comply with the requirements of § 314.50(i)(4) and (6) and § 314.94(a)(12)(vi) and (viii) regarding submission of an appropriate patent certification or statement. If the applicant submits an amendment certifying under § 314.50(i)(1)(i)(A)(4) or § 314.94(a)(12)(i)(A)(4) that the relevant patent is invalid, unenforceable, or will not be

infringed, and complies with the requirements of § 314.52 or § 314.95, the 505(b)(2) application or ANDA may be approved immediately upon submission of documentation of receipt of notice of paragraph IV certification under § 314.52(e) or § 314.95(e). The 45-day period provided for in section 505(c)(3)(C) and (j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act does not apply in these circumstances.

(3) Disposition of patent litigation--(i) Approval upon expiration of 30-month period or 7½ years from date of listed drug approval. (A) Except as provided in paragraphs (b)(3)(ii) through (viii) of this section, if, with respect to patents for which required information was submitted under § 314.53 before the date on which the 505(b)(2) application or ANDA was submitted to FDA (excluding an amendment or supplement to the 505(b)(2) application or ANDA), the applicant certifies under § 314.50(i) or § 314.94(a)(12) that the relevant patent is invalid, unenforceable, or will not be infringed, and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement within 45 days of receipt of the notice of certification from the applicant under § 314.52 or § 314.95, the 505(b)(2) application or ANDA may be approved 30 months after the later of the date of the receipt of the notice of certification by any owner of the listed patent or by the NDA holder (or its representative(s)) unless the court has extended or reduced the period because of a failure of either the plaintiff or defendant to cooperate reasonably in expediting the action; or

(B) If the patented drug product qualifies for 5 years of exclusive marketing under § 314.108(b)(2) and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement during the 1-year period beginning 4 years after the date of approval of the patented drug and within 45 days of receipt of the notice of certification from the applicant

under § 314.52 or § 314.95, the 505(b)(2) application or ANDA may be approved at the expiration of the 7½ years from the date of approval of the NDA for the patented drug product.

(ii) Federal district court decision of invalidity, unenforceability, or non-infringement. If before the expiration of the 30-month period, or 7½ years where applicable, the district court decides that the patent is invalid, unenforceable, or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the 505(b)(2) application or ANDA may be approved on:

(A) The date on which the court enters judgment reflecting the decision; or

(B) The date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid, unenforceable, or not infringed.

(iii) Appeal of Federal district court judgment of infringement. If before the expiration of the 30-month period, or 7½ years where applicable, the district court decides that the patent has been infringed, and if the judgment of the district court is appealed, the 505(b)(2) application or ANDA may be approved on:

(A) The date on which the mandate is issued by the court of appeals entering judgment that the patent is invalid, unenforceable, or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(B) The date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid, unenforceable, or not infringed.

(iv) Affirmation or non-appeal of Federal district court judgment of infringement. If before the expiration of the 30-month period, or 7½ years where applicable, the district court

decides that the patent has been infringed, and if the judgment of the district court is not appealed or is affirmed, the 505(b)(2) application or ANDA may be approved no earlier than the date specified by the district court in an order under 35 U.S.C. 271(e)(4)(A).

(v) Grant of preliminary injunction by Federal district court. If before the expiration of the 30-month period, or 7½ years where applicable, the district court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug product until the court decides the issues of patent validity and infringement, and if the court later decides that:

(A) The patent is invalid, unenforceable, or not infringed, the 505(b)(2) application or ANDA may be approved as provided in paragraph (b)(3)(ii) of this section; or

(B) The patent is infringed, the 505(b)(2) application or ANDA may be approved as provided in paragraph (b)(3)(iii) or (iv) of this section, whichever is applicable.

(vi) Written consent to approval by patent owner or exclusive patent licensee. If before the expiration of the 30-month period, or 7½ years where applicable, the patent owner or the exclusive patent licensee (or their representatives) agrees in writing that the 505(b)(2) application or ANDA may be approved any time on or after the date of the consent, approval may be granted on or after that date.

(vii) Court order terminating 30-month or 7½-year period. If before the expiration of the 30-month period, or 7½ years where applicable, the court enters an order requiring the 30-month or 7½-year period to be terminated, the 505(b)(2) application or ANDA may be approved in accordance with the court's order.

(viii) Court order of dismissal without a finding of infringement. If before the expiration of the 30-month period, or 7½ years where applicable, the court(s) enter(s) an order of dismissal,

with or without prejudice, without a finding of infringement in each pending suit for patent infringement brought within 45 days of receipt of the notice of paragraph IV certification sent by the 505(b)(2) or ANDA applicant, the 505(b)(2) application or ANDA may be approved on or after the date of the order.

(4) Tentative approval. FDA will issue a tentative approval letter when tentative approval is appropriate in accordance with this section. In order for a 505(b)(2) application or ANDA to be approved under paragraph (b)(3) of this section, the applicant must receive an approval letter from the Agency. Tentative approval of an NDA or ANDA does not constitute “approval” of an NDA or ANDA and cannot, absent an approval letter from the Agency, result in an approval under paragraph (b)(3) of this section.

(c) Timing of approval of subsequent ANDA. (1) If an ANDA contains a paragraph IV certification for a relevant patent and the ANDA is not that of a first applicant, the ANDA is regarded as the ANDA of a subsequent applicant. The ANDA of a subsequent applicant will not be approved during the period when any first applicant is eligible for 180-day exclusivity or during the 180-day exclusivity period of a first applicant. Any applicable 180-day exclusivity period cannot extend beyond the expiration of the patent upon which the 180-day exclusivity period was based.

(2) A first applicant must submit correspondence to its ANDA notifying FDA within 30 days of the date of its first commercial marketing of its drug product or the reference listed drug. If an applicant does not notify FDA, as required in this paragraph (c)(2), of this date, the date of first commercial marketing will be deemed to be the date of the drug product’s approval.

(3) If FDA concludes that a first applicant is not actively pursuing approval of its ANDA, FDA may immediately approve an ANDA(s) of a subsequent applicant(s) if the ANDA(s) is otherwise eligible for approval.

(d) Delay due to exclusivity. The Agency will also delay the approval of a 505(b)(2) application or ANDA if delay is required by the exclusivity provisions in § 314.108; section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter; section 505A of the Federal Food, Drug, and Cosmetic Act; or section 505E of the Federal Food, Drug, and Cosmetic Act. When the approval of a 505(b)(2) application or ANDA is delayed under this section and § 314.108; section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter; section 505A of the Federal Food, Drug, and Cosmetic Act; or section 505E of the Federal Food, Drug, and Cosmetic Act, the 505(b)(2) application or ANDA will be approved on the latest of the days specified under this section and § 314.108; section 527 of the Federal Food, Drug, and Cosmetic Act and § 316.31 of this chapter; section 505A of the Federal Food, Drug, and Cosmetic Act; or section 505E of the Federal Food, Drug, and Cosmetic Act, as applicable.

(e) Notification of court actions or written consent to approval. (1) The applicant must submit the following information to FDA, as applicable:

(i) A copy of any judgment by the court (district court or mandate of the court of appeals) or settlement order or consent decree signed and entered by the court (district court or court of appeals) finding a patent described in paragraph (b)(3) of this section invalid, unenforceable, or not infringed, or finding the patent valid and infringed;

(ii) Written notification of whether or not any action by the court described in paragraph (e)(1)(i) of this section has been appealed within the time permitted for an appeal;

(iii) A copy of any order entered by the court terminating the 30-month or 7½-year period as described in paragraph (b)(3)(i), (ii), (vii), or (viii) of this section;

(iv) A copy of any written consent to approval by the patent owner or exclusive patent licensee described in paragraph (b)(3)(vi) of this section;

(v) A copy of any preliminary injunction described in paragraph (b)(3)(v) of this section, and a copy of any subsequent court order lifting the injunction; and

(vi) A copy of any court order pursuant to 35 U.S.C. 271(e)(4)(A) ordering that a 505(b)(2) application or ANDA may be approved no earlier than the date specified (irrespective of whether the injunction relates to a patent described in paragraph (b)(3) of this section).

(2) All information required by paragraph (e)(1) of this section must be sent to the applicant's NDA or ANDA, as appropriate, within 14 days of the date of entry by the court, the date of appeal or expiration of the time for appeal, or the date of written consent to approval, as applicable.

(f) Forty-five day period after receipt of notice of paragraph IV certification--(1)  
Computation of 45-day time clock. The 45-day clock described in paragraph (b)(3) of this section as to each recipient required to receive notice of paragraph IV certification under § 314.52 or § 314.95 begins on the day after the date of receipt of the applicant's notice of paragraph IV certification by the recipient. When the 45th day falls on Saturday, Sunday, or a Federal holiday, the 45th day will be the next day that is not a Saturday, Sunday, or a Federal holiday.

(2) Notification of filing of legal action. (i) The 505(b)(2) or ANDA applicant must notify FDA in writing within 14 days of the filing of any legal action filed within 45 days of receipt of the notice of paragraph IV certification by any recipient. A 505(b)(2) applicant must



send the notification to its NDA. An ANDA applicant must send the notification to its ANDA.

The notification to FDA of the legal action must include:

- (A) The 505(b)(2) application or ANDA number.
  - (B) The name of the 505(b)(2) or ANDA applicant.
  - (C) The established name of the drug product or, if no established name exists, the name(s) of the active ingredient(s), the drug product's strength, and dosage form.
  - (D) A statement that an action for patent infringement, identified by court, case number, and the patent number(s) of the patent(s) at issue in the action, has been filed in an appropriate court on a specified date.
    - (ii) A patent owner or NDA holder (or its representative(s)) may also notify FDA of the filing of any legal action for patent infringement. The notice should contain the information and be sent to the offices or divisions described in paragraph (f)(2)(i) of this section.
    - (iii) If the 505(b)(2) or ANDA applicant, the patent owner(s), the NDA holder, or its representative(s) does not notify FDA in writing before the expiration of the 45-day time period or the completion of the Agency's review of the 505(b)(2) application or ANDA, whichever occurs later, that a legal action for patent infringement was filed within 45 days of receipt of the notice of paragraph IV certification, the 505(b)(2) application or ANDA may be approved upon expiration of the 45-day period (if the 505(b)(2) or ANDA applicant confirms that a legal action for patent infringement has not been filed) or upon completion of the Agency's review of the 505(b)(2) application or ANDA, whichever is later.
- (3) Waiver. If the patent owner or NDA holder who is an exclusive patent licensee (or its representative(s)) waives its opportunity to file a legal action for patent infringement within 45 days of a receipt of the notice of certification and the patent owner or NDA holder who is an

exclusive patent licensee (or its representative(s)) submits to FDA a valid waiver before the 45 days elapse, the 505(b)(2) application or ANDA may be approved upon completion of the Agency's review of the NDA or ANDA. FDA will only accept a waiver in the following form:

(Name of patent owner or NDA holder who is an exclusive patent licensee or its representative(s)) has received notice from (name of applicant) under (section 505(b)(3) or 505(j)(2)(B) of the Federal Food, Drug, and Cosmetic Act) and does not intend to file an action for patent infringement against (name of applicant) concerning the drug (name of drug) before (date on which 45 days elapse). (Name of patent owner or NDA holder who is an exclusive patent licensee) waives the opportunity provided by (section 505(c)(3)(C) or 505(j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act) and does not object to FDA's approval of (name of applicant)'s (505(b)(2) application or ANDA) for (name of drug) with an approval date on or after the date of this submission.

(g) Conversion of approval to tentative approval. If FDA issues an approval letter in error or a court enters an order requiring, in the case of an already approved 505(b)(2) application or ANDA, that the date of approval be delayed, FDA will convert the approval to a tentative approval if appropriate.

19. Amend § 314.108 as follows:

a. In paragraph (a):

i. Revise the introductory text and the definitions of “Approved under section 505(b)”, “Essential to approval”, and “New chemical entity”;

ii. Remove the definitions of “Active moiety”, “Date of approval”, and “FDA”; and

iii. Add in alphabetical order the definition of “Bioavailability study”; and

b. Revise the paragraph (b) heading and paragraphs (b)(2) through (5).

The revisions and addition read as follows:

§ 314.108 New drug product exclusivity.

(a) Definitions. The definitions in § 314.3 and the following definitions of terms apply to this section:

Approved under section 505(b) means an NDA submitted under section 505(b) and approved on or after October 10, 1962, or an application that was “deemed approved” under section 107(c)(2) of Public Law 87-781.

Bioavailability study means a study to determine the bioavailability or the pharmacokinetics of a drug.

\* \* \* \* \*

Essential to approval means, with regard to an investigation, that there are no other data available that could support approval of the NDA.

New chemical entity means a drug that contains no active moiety that has been approved by FDA in any other NDA submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

\* \* \* \* \*

(b) Submission of and timing of approval of a 505(b)(2) application or ANDA. \* \* \*

(2) If a drug product that contains a new chemical entity was approved after September 24, 1984, in an NDA submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, no person may submit a 505(b)(2) application or ANDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved NDA, except that the 505(b)(2) application or ANDA may be submitted after 4 years if it contains a

certification of patent invalidity or noninfringement described in § 314.50(i)(1)(i)(A)(4) or § 314.94(a)(12)(i)(A)(4).

(3) The approval of a 505(b)(2) application or ANDA described in paragraph (b)(2) of this section will occur as provided in § 314.107(b)(1) or (2), unless the owner of a patent that claims the drug, the patent owner's representative, or exclusive licensee brings suit for patent infringement against the applicant during the 1-year period beginning 48 months after the date of approval of the NDA for the new chemical entity and within 45 days after receipt of the notice described at § 314.52 or § 314.95, in which case, approval of the 505(b)(2) application or ANDA will occur as provided in § 314.107(b)(3).

(4) If an NDA:

(i) Was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act;

(ii) Was approved after September 24, 1984;

(iii) Was for a drug product that contains an active moiety that has been previously approved in another NDA under section 505(b) of the Federal Food, Drug, and Cosmetic Act; and

(iv) Contained reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application, for a period of 3 years after the date of approval of the application, the Agency will not approve a 505(b)(2) application or an ANDA for the conditions of approval of the NDA, or an ANDA submitted pursuant to an approved petition under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act that relies on the information supporting the conditions of approval of an original NDA.

(5) If a supplemental NDA:

(i) Was approved after September 24, 1984; and

(ii) Contained reports of new clinical investigations (other than bioavailability studies)

that were conducted or sponsored by the applicant that were essential to approval of the supplemental NDA, for a period of 3 years after the date of approval of the supplemental application, the Agency will not approve a 505(b)(2) application or an ANDA for a change, or an ANDA submitted pursuant to an approved petition under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act that relies on the information supporting a change approved in the supplemental NDA.

20. Amend § 314.125 as follows:

a. Remove the word “application” and add in its place “NDA” wherever it appears in paragraphs (a) introductory text, (a)(2), (b)(7), (9), (10), and (12), and (b)(14) through (18);

b. Remove the word “act” and add in its place “Federal Food, Drug, and Cosmetic Act” in paragraphs (a) introductory text and (b)(2), (11), and (18);

c. Revise the section heading and paragraph (b) introductory text; and

d. Add paragraph (b)(19).

The revisions and addition read as follows:

§ 314.125 Refusal to approve an NDA.

\* \* \* \* \*

(b) FDA may refuse to approve an NDA for any of the following reasons, unless the requirement has been waived under § 314.90:

\* \* \* \* \*

(19) The 505(b)(2) application failed to contain a patent certification or statement with respect to each listed patent for a drug product approved in an NDA that:

(i) Is pharmaceutically equivalent to the drug product for which the original 505(b)(2) application is submitted; and

(ii) Was approved before the original 505(b)(2) application was submitted.

\* \* \* \* \*

21. Amend § 314.127 as follows:

a. Remove the words “abbreviated application” and “abbreviated new drug application” wherever they appear and add in their place “ANDA” in paragraphs (a) introductory text, (a)(3) through (7), (a)(8)(ii)(A) introductory text, (a)(9) and (10), and (b);

b. Remove the word “act” wherever it appears and add in its place “Federal Food, Drug, and Cosmetic Act” in paragraphs (a)(3)(iii)(A)(2) and (a)(12);

c. Remove “officer of employee” and add in its place “officer or employee” in paragraph (b);

d. Revise the section heading and paragraphs (a) introductory text, (a)(2), (a)(8)(i) introductory text, and (a)(8)(ii)(B) and (C); and

e. Add paragraph (a)(14).

The revisions and addition read as follows:

§ 314.127 Refusal to approve an ANDA.

(a) FDA will refuse to approve an ANDA for a new drug under section 505(j) of the Federal Food, Drug, and Cosmetic Act for any of the following reasons, unless the requirement has been waived under § 314.99:

\* \* \* \* \*

(2) Information submitted with the ANDA is insufficient to show that each of the proposed conditions of use has been previously approved for the listed drug referred to in the ANDA.

\* \* \* \* \*

(8)(i) Information submitted in the ANDA or any other information available to FDA shows that:

\* \* \* \* \*

(ii) \* \* \*

(B) FDA will consider an inactive ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and will refuse to approve the ANDA unless it contains the same inactive ingredients, other than preservatives, buffers, and antioxidants, in the same concentration as the listed drug, and, if it differs from the listed drug in a preservative, buffer, or antioxidant, the ANDA contains sufficient information to demonstrate that the difference does not affect the safety or efficacy of the drug product.

(C) FDA will consider an inactive ingredient in, or the composition of, a drug product intended for ophthalmic or otic use unsafe and will refuse to approve the ANDA unless it contains the same inactive ingredients, other than preservatives, buffers, substances to adjust tonicity, or thickening agents, in the same concentration as the listed drug, and if it differs from the listed drug in a preservative, buffer, substance to adjust tonicity, or thickening agent, the ANDA contains sufficient information to demonstrate that the difference does not affect the safety or efficacy of the drug product and the labeling does not claim any therapeutic advantage over or difference from the listed drug.

\* \* \* \* \*

(14) For an ANDA submitted pursuant to an approved petition under § 10.30 of this chapter and § 314.93, an NDA subsequently has been approved for the change described in the approved petition.

\* \* \* \* \*

## PART 320--BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

22. The authority citation for part 320 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 371.

23. Section 320.1 is revised to read as follows:

### § 320.1 Definitions.

The definitions contained in § 314.3 of this chapter apply to those terms when used in this part.

24. Amend § 320.23 as follows:

- a. Revise the last sentence in paragraph (a)(1);
- b. Remove the word “shall” and add in its place the word “must” in paragraph (a)(2);
- c. Redesignate paragraph (b) as paragraph (b)(1); and
- d. Add paragraph (b)(2).

The revisions and additions read as follows:

### § 320.23 Basis for measuring in vivo bioavailability or demonstrating bioequivalence.

(a)(1) \* \* \* For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

\* \* \* \* \*

(b) \* \* \*



(2) For drug products that are not intended to be absorbed into the bloodstream, bioequivalence may be demonstrated by scientifically valid methods that are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

Dated: September 15, 2016.

Leslie Kux,

Associate Commissioner for Policy.

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